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Prevalence of and factors associated with gabapentinoid use and misuse among Texas Medicaid recipients

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Prevalence of and factors associated with gabapentinoid use and misuse among Texas Medicaid recipients

by

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Dedication

I dedicate this thesis to God Almighty, He is my unfailing strength and backbone. I also dedicate this thesis to my parents Mr. Moses and Mrs. Margaret Ibiloye for supporting me and giving me wings to fly. Finally, to my siblings; Toluwanimi and Fehintoluwa, and my son; Oreoluwa for believing in me, encouraging me and giving me reasons to remain persistent.

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Abstract

Prevalence of and factors associated with gabapentinoid use and misuse among Texas Medicaid recipients

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Gabapentinoids include drugs such as gabapentin and pregabalin, which are both approved by the FDA for the treatment of neuropathic pain, as well as other conditions. Rising prescribing trends and fatalities due to concurrent opioid overdose have created public health concerns regarding gabapentinoid misuse and abuse in the United States (US). Gabapentin prescriptions in the US increased from approximately 39 million (2012) to 67 million (2018) and pregabalin sales more than doubled from $2 billion (2012) to $4.4 billion (2016). This study aimed to assess the prevalence of and factors associated with gabapentinoid use and misuse.

This was a retrospective database study using Texas Medicaid prescription and medical claims from 1/1/12-8/30/16. Subjects were included if they: were between 18–63 years at index date, had at least one gabapentinoid prescription, and were continuously enrolled for 6 months pre-index and 12 months post-index. The dependent variable in this study was gabapentinoid misuse while age, gender, concurrent opioid use, neuropathic pain diagnoses and gabapentinoid type were independent variables.

Of included subjects (N=39,000), 0.2% (N=81) were gabapentinoid misusers. The majority (76.4%) of gabapentinoid users were 41–63 years with a mean±SD age of 48.2±10.7 years. Gabapentinoid misusers were significantly younger than gabapentinoid non-misusers (45.1±11.0 vs. 48.2±10.7, p=0.0084). The majority were female (68.1%), and a significantly higher proportion of males misused gabapentinoids compared to females (0.3% vs. 0.2%, p=0.0079). Over one-half (51.9%) of the study sample had neuropathic pain and gabapentinoid misuse was significantly higher in neuropathic pain patients compared to those without neuropathic pain (0.3% vs. 0.1%, p=0.0078). Over three-quarters (77.4%) of patients were using gabapentin, however, gabapentinoid misuse was significantly higher among pregabalin users compared to gabapentin users (0.4% vs. 0.2%, p=0.0003). About one-sixth (17.3%) of gabapentinoid users had at least 90 days of concurrent opioid use. However, there was no significant difference in gabapentinoid misuse among patients with concurrent opioid use compared to patients without (0.3% vs. 0.2%, p = 0.1440).

The prevalence of gabapentinoid misuse was low (0.2%) among Texas Medicaid recipients and younger age, male gender, neuropathic pain diagnosis and pregabalin use were significantly associated with gabapentinoid misuse.

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Chapter 1: Introduction

1.1 INTRODUCTION

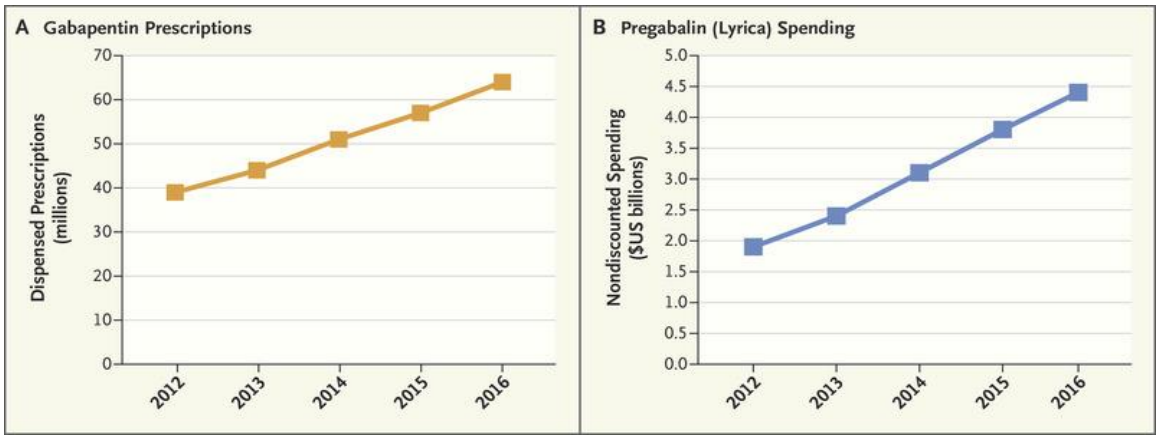
Pain is a common experience that interrupts the health and well-being of many people. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[1] Pain can be classified based on: 1) duration (acute and chronic); 2) intensity (mild, moderate and severe); and 3) site of damage (nociceptive and neuropathic). Acute pain is self-limiting and heals within days to weeks, while chronic pain lasts longer than three months and can worsen over time.[2, 3] Intensity refers to the impact or level of disruption caused by the pain experience. Mild pain is often treated with agents such as acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDS) while moderate to severe pain is often treated with opioids.[4, 5] Nociceptive pain occurs when there is damage or injury to the tissues while neuropathic pain occurs when there is damage to the nerves. The pain process in nociceptive pain differs from that in neuropathic pain, and they are managed using different types of agents. Nociceptive pain is generally managed with acetaminophen, NSAIDS and opioids while neuropathic pain management may require the use of antidepressants and anticonvulsants as well as opioids.[2, 6, 7, 8]

Gabapentin and pregabalin are two anticonvulsants used in managing neuropathic pain. They are referred to as gabapentinoids and are derived from the inhibitory neurotransmitter γ-aminobutyric acid (GABA). They act on pain by blocking the $\alpha_2\delta$ subunit of voltage-dependent calcium channels to decrease excitatory neurotransmission.[9] Gabapentin (Neurontin®) was approved by the Food and Drug Administration (FDA) in 1993 as an adjunct for epilepsy treatment in people over 12 years. This approval was

extended to children between 3 to 12 years in 2000, and approval for treating postherpetic neuralgia was granted in 2002. Pregabalin (Lyrica®) was approved for the treatment of diabetic peripheral neuropathy, and postherpetic neuralgia in 2004 and as adjunct treatment for partial onset seizures in adults in 2005. In 2007, pregabalin was approved for fibromyalgia.[10, 11,12] Aside from their approved conditions, gabapentin and pregabalin are also widely used 'off-label' in conditions such as bipolar disorder, restless leg syndrome, attention deficit hyperactivity disorder and other non-neuropathic pain.[10, 11]

Pregabalin is classified as a schedule V controlled substance by the Drug Enforcement Administration (DEA), but gabapentin is not classified as a controlled substance federally because it is believed to have low abuse potential.[13] However, both pregabalin and gabapentin have come under public health scrutiny because their utilization rates have increased substantially within the last few years. In the United States, about 64 million prescriptions were written for gabapentin in 2016, which represents a 49% increase since 2011 (Figure 1.1).[14] In 2018, gabapentin prescriptions rose to 67 billion, which makes gabapentin the sixth most prescribed medication in the United States.[15] Similarly, pregabalin sales increased from $2 billion in 2012 to $4.4 billion in 2016 (Figure 1.1).[14] This trend is not limited to the United States alone, as gabapentin and pregabalin prescriptions increased by 350% and 150% respectively over 5 years in the United Kingdom.[16, 17] This increase in the use of gabapentinoids is not necessarily explained by a proportionate increase in neuropathic pain diagnosis; rather, it is believed that a response to the opioid crisis is partly responsible for this rise.[14]

Figure 1.1: Rise in gabapentin prescriptions and pregabalin spending between 2012 and 2016[14]



It has been purported that the opioid crisis started in the 1990s after physicians were reassured of the safety and low addiction potential of opioids by the pharmaceutical industry. This led to an increase in the use of opioids in pain management, and by 2011, 238 million prescriptions were being written for opioids yearly. The ease of access and widespread availability of opioids led to their diversion, misuse and abuse. Consequently, opioid-related fatalities quadrupled between 1991 and 2010.[18] Fatalities from opioid overdose continued to rise, with approximately 42,000 and 48,000 fatalities due to opioids alone in 2016 and 2017, respectively.[19, 20] Various federal and state government agencies have responded to the opioid crisis by developing guidelines and regulations as well as passing legislation to restrict unwarranted opioid use.[21, 22, 23] In response to the opioid crisis and restrictions, clinicians have employed various strategies to manage pain while reducing opioid consumption.[14, 24] One of such strategies is the concurrent use of medications such as gabapentinoids with opioids.[24]

The rise in gabapentinoid use is a reason for public health concern because research shows that the risk for respiratory depression and opioid-related death increases by 60%

when gabapentinoids are used in combination with opioids.[13] Some studies have shown that people abuse gabapentinoids for the purpose of potentiating the "high" they get from opioids. Similarly, post-mortem studies have established the increasing presence of gabapentin in overdose-related fatalities. [25, 26]

While current evidence on the existence and effect of gabapentin misuse has not led to its reclassification as a controlled substance by the DEA, some states have taken regulatory and legislative action on gabapentin use. Kentucky became the first state to reclassify gabapentin as a schedule V controlled substance in July 2017. The reclassification was in response to the presence of gabapentin in 93 out of 407 (22.9%) cases of overdose related deaths in one county alone, as well as in one-third of all drug related deaths across Kentucky in 2016.[13, 27, 28] West Virginia, Tennessee, Michigan, Virginia, North Dakota and Alabama have followed Kentucky's lead by reclassifying gabapentin to schedule V medication. [29, 30, 31, 32, 33, 34] In addition to this, states such as Minnesota, Ohio, Wyoming, Massachusetts, Nebraska, New Jersey and Kansas have added gabapentin to their prescription drug monitoring programs (PDMPs).[13] As of 2020, Texas has not reclassified gabapentin or placed it on their PDMP.

Although evidence shows that both gabapentin and pregabalin can be misused or abused for their opioid potentiating effects, not much is known about the scope of their misuse nationally. To the author's knowledge, only commercial databases in the United States have been studied to evaluate gabapentin prescribing, and to establish its prevalence and abuse potential.[25, 35] However, these studies excluded Medicare and Medicaid patients. To the author's knowledge, this study would be the first to be conducted using a state Medicaid population. It would also provide useful data concerning the prevalence of gabapentinoid misuse in Texas, which, to date, has not been reported.

Chapter 2: Literature review

2.1 CHAPTER OVERVIEW

This chapter contains the literature review of the major concepts of this study. The first part gives a description on the definition, impact, cost and management of pain. The second part describes the use of opioids in pain management and the consequent opioid crisis. Note that the second part of the literature review is described in some detail to better explain the reasons for the shift to gabapentinoid use. The third part discusses the use of gabapentinoid in pain management following the opioid crisis and restrictions on opioid use. The final section further elaborates on the significance of this study as described in Chapter 1.

2.2 PAIN

2.2.1 Definition, impact and cost of pain

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] This means pain is a multidimensional experience, affecting the nervous system, emotions and cognition.[36] This effect on not just the biological framework of a person, but also on both the emotions and cognition, make pain a subjective experience, and as such, two people can experience and respond to the same type of pain in varying degrees.[37, 38, 39] This varying perception and response to pain is a function of individual pain thresholds, genetic, environmental and psychological factors, and research also shows that gender and ethnicity can impact pain perception, tolerance and response to treatment.[37, 38, 40, 41, 42]

Despite these differences in perception and response, pain is: associated with health care resource utilization; a foremost cause of disability; and a significant driver of health care costs.[42, 43] A study conducted using the 2012 National Health Interview Survey (NHIS) data (N = ~ 226 million), revealed that up to 126 million adults (55.8%) reported some pain in the three-month period prior to the survey, with 25.3 million adults (11.2%) experiencing chronic pain, and 23.4 million (10.3%) reporting a lot of pain. This report was also used to rank patients into categories of pain severity, with 14.4 million adults (6.4%) in category 4 pain (highest level of pain) and 25.4 million adults (11.3%) in category 3.[44] Another analysis of the prevalence of chronic pain and high-impact chronic pain from the 2016 NHIS data, shows that about 20.4% (50 million) of adults were living with chronic pain in 2016 and 8% (19.6 million) had high-impact chronic pain.[45] High-impact chronic pain (HICP) is a new concept of classifying chronic pain based on both duration and severity, and is used to describe a subset of the chronic pain population that is more severely impacted in terms of disability, and mental and cognitive impairment.[46]

Consequently, health care expenditures for treating pain are estimated to range from $560 billion to $635 billion annually, which is greater than the yearly costs of heart disease ($309 billion), cancer ($243 billion) and diabetes ($188 billion). This amount is also greater than the combined cost of cancer and heart disease ($309 billion + $243 billion), cancer and diabetes ($243 billion + $188 billion) or diabetes and heart disease ($309 billion + $188 billion).[47, 48]

The impact of pain is not just observed in rising economic costs, but also in a person's overall quality of life, as pain has a deleterious effect on a patient's mood, capability, ability to gain employment, as well as on social and familial relationships.[49] These multifaceted effects and consequences of pain have made it one of the most significant crises of healthcare in America today.

2.2.2 Classification of pain

There are various ways of classifying pain, but for the purpose of this review, pain will be classified according to its duration, intensity and site of damage.

2.2.2.1 Duration

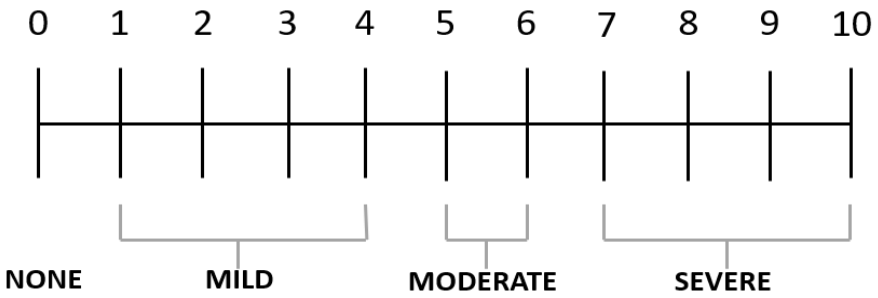
Pain can be classified into acute or chronic pain, based on the time it takes for the underlying cause to be resolved. Acute pain is the normal physiological response to injurious chemical, mechanical or thermal stimulus. It occurs when pain receptors, known as nociceptors are activated at the site of injury or damage. It serves as a signal that an injury has occurred, and further attention or examination is needed. Acute pain is self-limiting and heals within days to weeks.[2, 3]

Chronic pain is defined as "pain that persists or recurs for more than three months."[50] The difference between acute and chronic pain is in the duration and underlying pain mechanism. Acute pain has a sudden onset and resolves within a few days to weeks, while chronic pain is persistent and exists beyond the healing period associated with acute pain.[2] This persistence can occur as a result of changes to the nervous system that chronic pain causes, which prevents positive adaptation, and can lead to worsening pain as time passes. [51] Chronic pain is increasingly recognized as a significant public health challenge and has been linked to other conditions that impair quality of life, such as anxiety, depression, opioid dependence, limited mobility and it is also recognized as a risk factor for suicide. It is estimated that chronic pain alone affects about 50 million Americans, and higher prevalence of chronic pain is seen in women, older people and people of lower socioeconomic status.[40, 45, 12, 51]

2.2.2.2 Intensity

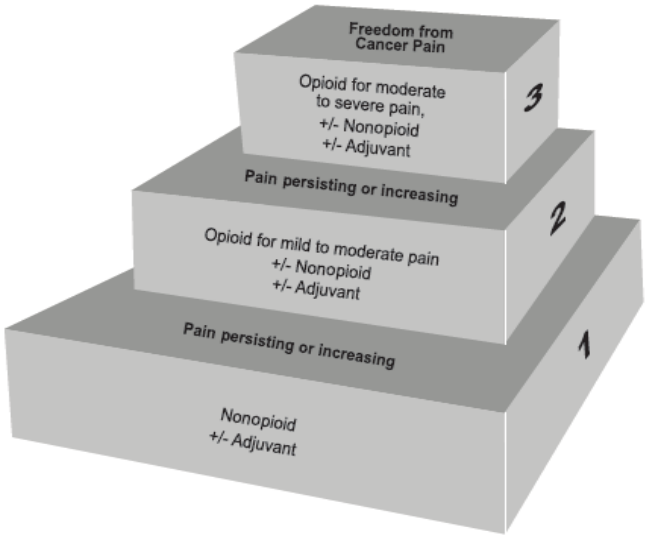
Pain can also be classified based on its intensity as either mild, moderate or severe. Pain intensity is determined through various measures and scales that attempt to quantify pain and assess its impact on function. Using a scale of 0 to 10, mild pain can be classified as pain with an intensity level of 1 to 4 and is considered to have relatively low impact on a patient's functioning, while moderate pain is classified as pain between 5 and 6, and severe pain is regarded as 7 to 10 (Figure 2.1).[5]

Figure 2.1: Pain intensity numeric rating scale[5, 52]



The World Health Organization (WHO) analgesic ladder is used to make clinical decisions regarding pain treatment. This ladder is based on classifying pain according to its intensity (Figure 2.2). Mild pain is treated with agents such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS) and adjuvants while moderate to severe pain is treated with opioids in addition to the agents for mild pain. These agents will be described in section 2.2.4.2.[5, 4]

Figure 2.2: World Health Organization analgesic ladder[53]



2.2.2.3 Site of damage

Pain can be broadly categorized into nociceptive or neuropathic based on the site of damage. Pain resulting from damage to the tissues is referred to as nociceptive pain, while neuropathic pain results from damage to the nervous system.

Nociceptive pain refers to pain that occurs as a result of damage or injury to the tissues.[6] The term nociception describes the processes involved in pain, starting from the stimulus or damage, the transduction of such stimulus to impulses and the transmission of impulses to the spinal cord and brain, which leads to a conscious awareness of pain.[2,19,20] Nociceptive pain serves as a protection, by creating awareness of and need to care for an injury or damage, so that healing can occur.[6, 54] Subtypes of nociceptive pain include visceral pain (pain in organs and smooth muscles) and somatic pain (cutaneous, myofascial and joint pain).[2]

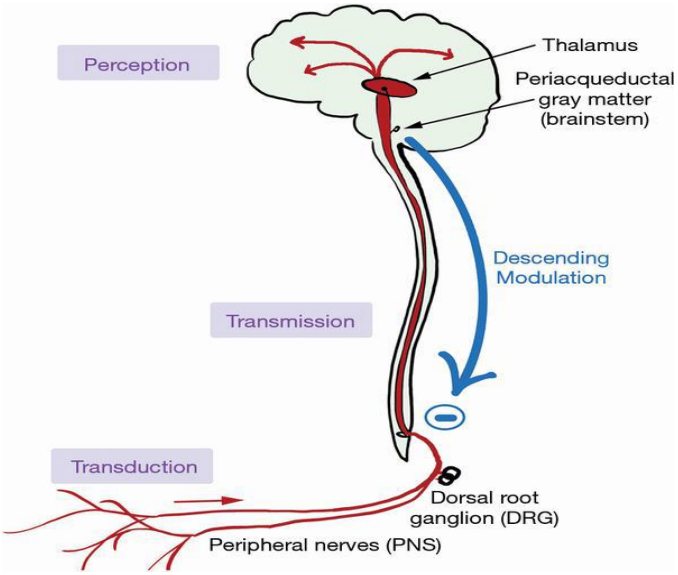
Neuropathic pain occurs when there is a sensory, motor or autonomic damage to or dysfunction in the nervous system. Unlike nociceptive pain, it is independent of a

stimulus and does not have a protective function.[7, 25] It is commonly described as a burning, shooting, stabbing, tingling or prickling feeling.[55] Its severity surpasses other types of pain, and conventional pain treatment may not be effective; hence, treatment for neuropathic pain usually includes antidepressants, anticonvulsants and opioids.[56,8] Subtypes of neuropathic pain include postherpetic neuralgia, diabetic neuropathic pain, HIV-related neuropathic pain, neuropathic lower back pain, cancer-related neuropathic pain, complex regional pain syndrome and postoperative neuropathic pain.[8]

2.2.3 Pain (nociception) processes

The pain process refers to pathways through which injurious stimuli are recognized. The following four pathways are involved in the detection of pain: transduction, transmission, perception and modulation (Figure 2.3).[54]

Figure 2.3: Nociceptive pain process [57]



2.2.3.1 Transduction

Transduction occurs when receptors, called nociceptors convert an external pain stimulus into nerve impulses.[58] When tissue injury or damage occurs, various types of sensitizing chemicals and impulses are released by cells to excite nerve endings and start the process of wound healing. Nociceptors receive these chemical, mechanical and thermal impulses, and convert them to electrical signals which can then be transmitted to the spinal cord. Local anesthetics and antiepileptics, are useful at this level of pain mechanism, because they prevent those electrical signals from being formed and/or transmitted.[6, 54]

2.2.3.2 Transmission

During transmission, the electrical signals created through transduction are relayed along the peripheral nerve. Two peripheral nerve fibers are involved in this process, the A-deltas and the C-fibers. The A-delta fibers are subdivided into Type I and Type II nociceptors. Type I have a strong response to chemical and mechanical stimuli, but can also respond to high thermal stimuli, while the Type II respond primarily to thermal stimuli.[54] The A-delta fibers transmit these chemical, mechanical or thermal signals rapidly, and are the cause of localized, sharp, stabbing pain that is felt initially after an injury. C-fibers generally respond to all types of stimuli (i.e., chemical, mechanical and thermal), however there is a subgroup that respond selectively to either thermal or mechanical stimuli. C-fibers transmit pain signals slower than A-delta fibers, and are responsible for generalized, dull, throbbing pain that exists after injury occurs.[6, 54]

2.2.3.3 Perception

Perception refers to the process that occurs in the somatosensory cortex to make pain recognizable by a conscious person. At this stage, the limbic system mediates a

person's affective-emotional response to pain and determines how a person perceives their pain.[6]

2.2.3.4 Modulation

Modulation refers to the ability of the brain to increase or decrease pain impulses. In modulation, the response to pain is not directly proportional to the stimulus because pain includes both sensory and affective elements.[2] The modulation of pain is a function of somatosensory inputs, emotional and motivational components. This means that the ability to "block out" or "feel" pain can be influenced by mechanisms other than those from the injury, as well as a person's attention to or distraction from the pain.[6, 54] The production of excitatory or inhibitory neurotransmitters by the body can upregulate or downregulate pain impulses. Descending pathways that extend from the brain to the dorsal horn in the spinal cord, can also exaggerate or weaken the impulses to the brain.[19, 20] Production and release of excitatory neurotransmitters, such as glutamate, substance P, and calcitonin gene-related peptide (CGRP) can increase sensitivity to pain impulses, while the release of inhibitory neurotransmitters like γ-aminobutyric acid (GABA), serotonin, endorphins and norepinephrine can decrease sensitivity to pain.[19, 20, 4]

2.2.4 Management and treatment of pain

The focus of this research is to evaluate the use and misuse of gabapentinoids in pain management; however, other methods of pain management, particularly opioids will be reviewed, as opioid use is a risk factor for gabapentinoid misuse.[59, 60, 61] Strategies to address pain include both pharmacological and non-pharmacological approaches.

2.2.4.1 Non-pharmacological intervention

Non-pharmacological interventions include strategies that are used alone or in conjunction with pharmacological therapy to ease pain. They include transcutaneous electrical nerve stimulation, acupuncture, massage and exercise.[62, 63]

2.2.4.2 Pharmacological intervention

Pharmacological therapy for pain can be broadly divided into three areas: non-opioid analgesics, opioid analgesics and adjuvants such as antidepressants, anticonvulsants and corticosteroids.[64] Non-opioid analgesics include acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), which are the agents recommended in the first step of the WHO analgesic ladder (Figure 2.2). The ladder is a step-wise approach to managing pain, with non-opioids recommended as the first step for mild pain, weak opioids for moderate pain and strong opioids for severe pain. This step-wise approach has been used to develop various evidence-based guidelines for managing different types of pain. However, for conditions such as neuropathic pain, the use of other medications such as antidepressants and anticonvulsants (e.g., gabapentin and pregabalin), as well as opioids have been recommended.[65, 66] The choice of pharmacological treatment is determined after weighing the benefits and risks, particularly regarding opioid therapy.

2.3 THE USE OF OPIOIDS IN PAIN MANAGEMENT

2.3.1 Introduction

Opioids refer to a class of drugs that act mainly on the mu opioid receptor to produce analgesic effects. In addition to mu, the other target receptors are delta, kappa and

nociception opioid receptors. Opioids include compounds such as morphine and codeine, which are derived directly from the opium poppy plant, as well as synthetic analogues such as oxycodone, hydrocodone and buprenorphine.[67, 68] Opioids are widely used to treat moderate to severe pain, and about 58 opioid prescriptions were written for every 100 Americans in 2017.[69] Opioids are also commonly used for managing cancer pain, and pain due to terminal diseases, such as AIDS and degenerative diseases. Some of their benefits include: decreased pain, better pain management, improved physical function and increased quality of life.[70] However, despite their usefulness in pain management, opioids also have a variety of complications such as sedation, constipation, nausea, vomiting, tolerance, dependence, respiratory depression, hyperalgesia, immunosuppression, hormonal changes, risk of misuse and abuse as well as fatalities due to overdose.[71, 72] Therefore, alternative analgesic options should be considered before opioid use, and when opioid use is inevitable, treatment should start with the lowest effective dose and titrated upwards if needed.[72]

Opioid agonists produce potent anti-nociceptive action through binding to opioid receptors within the central and peripheral nervous system.[73] These receptors modulate pain, regulate the reinforcement and reward system, regulate mood and respond to stress.[74] The type of receptor and affinity of the opioid to the receptor contributes to the extent of analgesia produced. Opioids act on the transmission stage of the pain process, by indirectly stimulating and activating descending inhibitory neurons. This increase in neuronal traffic leads to a decrease in the transmission of pain from the periphery to the brain.[75, 76]

2.3.2 Classification of opioids

As shown in the WHO analgesic ladder (Figure 2.2), opioids are prescribed based on pain intensity and are classified into strong, intermediate and weak. Strong opioids include morphine, pethidine, fentanyl, methadone and oxycodone; intermediate opioids include buprenorphine, pentazocine and butorphanol; while weak opioids include codeine and tramadol (Table 2.1).[77]

Opioids can also be classified as either endogenous or exogenous. Endogenous opioids are those created by the body, and they include, endorphins, enkephalins, dynorphins and endomorphins.[68] Exogenous opioids can be subdivided into naturally occurring compounds like morphine, semi-synthetic opioids such as oxycodone, hydromorphone and hydrocodone, and synthetic opioids like methadone, tramadol and fentanyl (Table 2.1).

A third form of classification is based on their interaction with opioid receptors into full agonists, partial agonists and antagonists. Full and partial agonists bind to receptors but produce different levels of receptor activation or response. Full agonists have high efficacy and produce the maximum activation possible when they bind to a receptor. Partial agonists on the other hand produce sub-maximal response compared to a full agonist even when they have similar or higher binding affinity to the receptor. Consequently, a partial agonist can display antagonistic effects in the presence of a full agonist by competing with the full agonist for receptor occupancy. This reduces the ability of the full agonist to elicit the maximum response it is capable of producing when used alone. Examples of full agonists include morphine, fentanyl and oxycodone and partial agonists include buprenorphine, pentazocine and butorphanol (Table 2.1).[78, 79] Antagonists refer to medications that block the activity of opioids, by competing for opioid receptors because they have higher binding affinity than agonists but do not elicit receptor activation. This

makes them useful for addressing opioid dependence and overdose, examples include naloxone and naltrexone (Table 2.1).[77]

Table 2.1: Classification of opioids[68, 77]

Opioids	**Strength**	**Chemical Structure**	**Receptor Interaction**
Morphine	Strong	Naturally occurring	Full agonist
Oxycodone	Strong	Semi-synthetic	Full agonist
Hydrocodone	Strong	Semi-synthetic	Full agonist
Hydromorphone	Strong	Semi-synthetic	Full agonist
Fentanyl	Strong	Synthetic	Full agonist
Methadone	Strong	Synthetic	Full agonist
Pethidine	Strong	Synthetic	Full agonist
Meperidine	Strong	Synthetic	Full agonist
Buprenorphine	Intermediate	Semi-synthetic	Partial agonist
Pentazocine	Intermediate	Synthetic	Partial agonist
Butorphanol	Intermediate	Synthetic	Partial agonist
Codeine	Weak	Naturally occurring	Full agonist
Tramadol	Weak	Synthetic	Partial agonist
Naloxone	-	Semi-synthetic	Antagonist
Naltrexone	-	Semi-synthetic	Antagonist

2.3.3 Uses

Opioids are available as both immediate and extended release formulations. Immediate release formulations are used for both acute and chronic pain, while extended release formulations are used for chronic pain when immediate release opioids are no longer adequate.[80, 81] Despite the popular use of opioids in managing chronic pain, controversy exists about their efficacy, as there is limited evidence on their superiority over non-opioids in chronic pain management.[82, 83]

Opioids are used to manage various types of pain such as dental, cancer, muscle, joint, back, abdominal, post-traumatic and post-surgical pain.[84, 85] They are also used in addition to adjuvant analgesics for neuropathic pain; however, their use is controversial as some types of neuropathic pain may be non-responsive to opioids.[86] Opioids can also be combined with other drugs and used for non-pain treatment, for example, codeine and hydrocodone can be combined with other drugs to treat cough.[87]

2.3.4 Guidelines for the use and prescription of opioids

The Centers for Disease and Control (CDC) guidelines for management of chronic pain (released in 2016) have three main objectives;[88]

"1. Improve communication between providers and patients about the risks and benefits of opioid therapy for chronic pain.

2. Improve the safety and effectiveness of pain treatment.

3. Reduce the risks associated with long-term opioid therapy, including opioid use disorder and overdose."

The key concepts of the guidelines include: considering non-pharmacologic or non-opioid therapy before opioids, establishing treatment goals before initiating opioid therapy,

assessing patient's risks and benefits, using immediate-release opioids at the start of opioid therapy instead of extended or long-acting opioids for either acute or chronic pain, using lowest effective dose and titrating upwards slowly avoiding an increase of ≥ 90 morphine milligram equivalents (MME)/day, reviewing controlled substances history, using urine drug testing, avoiding concurrent benzodiazepine use and providing treatment for opioid use disorder.[44]

Various states also have specific opioid guidelines, with most of them sharing recommendations similar to the CDC guidelines, such as, using non-opioid therapy as first option for acute pain, and where opioid use is warranted, using the lowest effective dose. Others include avoiding the use of long-term opioids for acute pain, including appropriate counselling and assessment strategies when opioids are used for chronic pain, avoiding the concurrent use of opioids with benzodiazepines, as well as providing education on opioid overdose.[89, 90] Most of these guidelines were established following the opioid crisis.

2.3.5 The opioid crisis

It has been purported that the opioid epidemic started in the 1990s after physicians were reassured of the safety and low addiction potential of opioids by the pharmaceutical industry. This led to an increase in the prescription and use of opioids in pain management, and by 2011, 238 million prescriptions were being written for opioids annually. This resulted in diversion and misuse of opioids, and the fatality rate from opioid overdoses quadrupled between 1991 and 2010.[18] In 2010, over 16,000 people died from opioid overdoses, and within six years, the number more than doubled, with over 42,000 Americans reportedly dying from opioid overdoses in 2016 alone.[18, 19] In addition to the fatalities, an estimated 11.4 million people misused prescription opioids, 2 million misused

opioids for the first time and 2.1 million people had an opioid use disorder in 2016 alone.[88, 19] In response to the escalation of these issues, in 2017, the US Department of Health and Human Services declared the opioid crisis a public health emergency and released a five-point strategy to address the crisis (see Section 2.3.6 for more details).[21]

In addition to fatalities, other consequences of opioid misuse and abuse include neonatal abstinence syndrome, anxiety, depression, lowered motivation and productivity, impaired social functioning, structural changes to the brain, as well as bleeding disorders.[91, 92, 93] The opioid crisis also had a significant economic impact, as costs related to the opioid crisis in 2016 alone were $95.8 billion with an estimated total of over $1 trillion since 2001.[94] All of these factors have led to various responses and interventions at the federal, state and local levels to address the crisis.

2.3.6 Restrictions and legislation to address the opioid crisis

Some of the responses to the opioid crisis have been the creation of guidelines, legislation and programs to regulate and monitor opioid prescribing and use. As part of the federal government's efforts to reduce opioid related deaths, the Department of Health and Human Services released a five-point strategy in 2017 aimed at: 1) increasing access to prevention, treatment and recovery services, 2) increasing the availability and access to opioid overdose-reversing medications, 3) strengthening the reporting and collection of public health data, 4) supporting research on pain and addiction, and 5) advancing research that can provide evidence based pain management strategies, and reduce unnecessary use of opioids.[21]

The Drug Enforcement Agency (DEA) uses a three-part approach to combat the opioid crisis, which includes: 1) employing law enforcement actions against drug cartels,

2) using diversion control enforcement activities and 3) engagement with DEA registrants, pharmaceutical businesses and practitioners, as well as community-based outreach.[95]

States have also responded to the crisis by enacting laws and policy-based interventions. State Prescription Drug Monitoring Programs (PDMPs) use electronic databases to track prescription and dispensing patterns for specific medications. The use of PDMPs has facilitated tracking of opioid prescribing and dispensing, reduced the ease of doctor and pharmacy shopping for opioids, as well as decreased opioid misuse and diversion.[22, 23] In addition, about 30 states have implemented stricter opioid control measures, by imposing various types of legal limitations on opioid prescribing.[96] There are also various recommendations and grants by community led partnerships and coalitions, aimed at supporting these federal and state government strategies.[97, 98]

Pharmacological strategies used to combat opioid use disorder and fatalities include naloxone distribution programs and Medication-Assisted Treatment (MAT).[99] Naloxone is an opioid antagonist that can reverse respiratory depression caused by opioid overdose. It does not have any euphoric effect and is not effective for non-opioid related overdoses. Currently, all 50 states and Washington DC have passed legislation that facilitates access and distribution of naloxone.[100, 101, 102,103] MAT involves the use of two opioid agonists/partial agonist, methadone and buprenorphine, in conjunction with naltrexone to manage opioid withdrawal symptoms, decrease opioid cravings and block the effect of opioids. These medications are used in conjunction with counselling and behavioral therapies for a holistic approach to recovery and prevention of relapse.[99, 104, 105]

2.3.7. Impact of opioid restriction on the use of non-opioid analgesics for pain management

The need to properly manage pain while addressing the challenge of opioid misuse and abuse have led to providers exploring other pain management strategies, such as concurrent use of non-opioid medications (e.g., gabapentinoids and muscle relaxants). The goal of this strategy is to reduce the use of and dependence on opioid therapy, by using alternative therapies that have relatively liberal restrictions on their use.[14, 60]

Gabapentin and pregabalin are both approved by the FDA for neuropathic pain. However, studies show that there has been an upward trend in their prescription rate. In England over the last 5 years, gabapentin and pregabalin use have increased by 350% and 150%, respectively.[106] In the United States, about 64 million prescriptions were written for gabapentin in 2016, which represents a 49% increase since 2011. Similarly, pregabalin sales increased from $2 billion in 2012 to $4.4 billion in 2016.[14, 16] The increase in risk of respiratory depression and subsequent fatalities when gabapentinoids are used alongside opioids, as well as the growing evidence for their misuse and abuse, have led to public health concerns regarding the use of gabapentinoids in pain management.[107]

2.4 USE AND MISUSE OF GABAPENTINOIDS

2.4.1 Introduction

Gabapentinoids refer to a class of drugs that are derived from the inhibitory neurotransmitter γ-aminobutyric acid (GABA). They are also referred to as $\alpha_2\delta$ ligands, as they block the $\alpha_2\delta$ subunit of voltage-dependent calcium channels to decrease excitatory transmission. They include drugs such as pregabalin, gabapentin, as well as gabapentin enacarbil, which is a gabapentin prodrug.

Gabapentin and pregabalin were the first $\alpha_2\delta$ ligands to be synthetized for use in epilepsy treatment but were later found to be effective in treating other conditions.[108] Currently they are both approved by the FDA for the treatment of neuropathic pain among other conditions. Their efficacy in neuropathic pain is assumed to result from the reduction in calcium influx and subsequent inhibition of excitatory neurotransmitter release that occurs when they bind to the $\alpha_2\delta$ subunit of voltage-dependent calcium channels.[9]

Despite their structural similarity, pregabalin is six times more potent in its binding activity to the $\alpha_2\delta$ subunit than gabapentin. It is also absorbed three times faster than gabapentin and has greater bioavailability than gabapentin.[9, 109] The bioavailability of gabapentin reduces from about 60% following a 900mg dose/day to 33% and 27% following a 3600mg and 4800mg dose/day, respectively.[110] However, pregabalin maintains a bioavailability of about 90% irrespective of the dose.[9]

Pregabalin is also considered to have a higher potential for misuse and abuse than gabapentin, and as such was categorized as a schedule V drug by the DEA before its release to the market. Gabapentin was considered to have a low risk of abuse or addictive effect and was not listed as a controlled substance. However, recent research indicates gabapentin may potentiate the euphoric effect of opioids, and increase the risk of respiratory depression and opioid-related mortality.[60] This discovery led Kentucky, West Virginia, Tennessee, Michigan and Virginia to list gabapentin as a schedule V controlled substance.[30,31, 32, 111] Other states are currently establishing legislative regulations to monitor gabapentin use, drafting policies or gathering data to support decision making. [60]

The maximum recommended daily dosage for pregabalin varies between 450mg for fibromyalgia to 600mg for diabetic neuropathy, postherpetic neuralgia and partial onset seizures. For gabapentin, the maximum daily dose is 1800mg for postherpetic neuralgia

and 3600mg for partial onset seizures. Side effects of gabapentin and pregabalin include fatigue, dizziness, nausea, somnolence and ataxia.[112, 110]

2.4.2 History

Gabapentin (Neurontin®) was approved in 1993 as an adjunct treatment for partial complex seizures in people over 12 years old, and this approval was extended to include children from age 3 to 12 in 2000. In 2002, gabapentin was approved for the treatment of postherpetic neuralgia.[113] Generic gabapentin became available in 2004 after the first generic equivalent of Neurontin® was approved by the FDA in 2003.[10] Pregabalin (Lyrica®) was approved for the treatment of diabetic peripheral neuropathy and postherpetic neuralgia in 2004, adjunct treatment of partial onset seizures in 2005, fibromyalgia in 2007, and neuropathic pain associated with spinal cord injury in 2012. In 2012, an extended release version was approved for diabetic neuropathy and postherpetic neuralgia.[11, 12] The first generic pregabalin was approved by the FDA in 2019.[114] In addition to these approved conditions, gabapentin and pregabalin are also used off label for conditions such as bipolar disorder, attention deficit hyperactivity disorder, restless leg syndrome, trigeminal neuralgia and other non-neuropathic pain.[115]

2.4.3 Guidelines for use in neuropathic pain

2.4.3.1 Gabapentin use in postherpetic neuralgia

Treatment should begin as a single dose of 300mg on the first day, increased to 600mg (300mg twice) on the second day and 900mg (300mg thrice) on the third day. This can be titrated upwards to a maximum of 1800mg a day (600mg three times daily) for

postherpetic neuralgia. However, for partial-onset seizures, the dose can be titrated to a maximum of 3600mg. The above recommendation is for patients with normal renal function, measured as creatinine clearance above 60ml/min. For patients with impaired renal function, the dose is calculated based on their creatinine clearance (Table 2.2).[116]

Table 2.2: Gabapentin dosage based on renal function[116]

Creatinine clearance (ml/min)	**Total daily dose (mg/day)**
≥ 60	900 to 3600
30 to 59	400 to 1400
15 to 29	200 to 700
<15	100 to 300

2.4.3.2 Pregabalin use in postherpetic neuralgia

Treatment should begin with a dose of 75mg twice daily or 50mg thrice daily (150mg/day). This can be increased to a dose of 300mg/day within a week. If a dose of 300mg/day is insufficient after 2 to 4 weeks, then treatment may be titrated up to 300mg twice daily or 200mg thrice daily (600mg/day). In patients with impaired renal function, the dose administered is based on creatinine clearance (Table 2.3).[112]

2.4.3.3 Pregabalin use in diabetic neuropathy

Treatment should begin with a dose of 50mg taken thrice daily (150mg/day). This can be increased to the maximum recommended dose of 100mg thrice daily (300mg/day). In patients with impaired renal function, the dose administered is based on creatinine clearance (Table 2.3).[112]

Table 2.3: Pregabalin dosage based on renal function[112]

Creatinine clearance (ml/min)	Total daily dose (mg/day)
≥ 60	150 to 600
30 to 59	75 to 300
15 to 29	50 to 150
<15	25 to 75

2.4.5 Gabapentinoid misuse

2.4.5.1 Introduction

Drug misuse can be defined as the use of a medication for a purpose that is inconsistent with medical or legal guidelines. Drug misuse can refer to using another person's medication, administering the medication through an unprescribed route, or using doses higher than prescribed.[117, 118] While there may be some overlap in defining drug misuse and abuse, it is important to note that drug misuse and abuse refer to two different ideas.[117, 119] One of the reasons misuse and abuse might be incorrectly used interchangeably is because various health agencies and organizations define these terminologies differently, so a wide range of operational definitions for misuse and abuse exist.[119, 120, 121] However, a majority of the definitions of drug misuse tend to restrict the term "misuse" to the improper use of prescription or over-the-counter medications, for therapeutic purposes or with therapeutic intent.[117, 119, 122] Abuse, on the other hand is used to refer to the use of prescribed or illicit substances for nontherapeutic purposes or to obtain certain mind altering effects, such as sedative, anxiolytic or euphoric effects.[117, 119, 123]

The misuse of prescription opioids, CNS depressants and stimulants has been established as a public health concern in the United States. In 2017, an estimated 18 million people misused prescription medications at least once within the past year, and 2 million people misused prescription pain relievers for the first time within the past year according to the Substance Abuse and Mental Health Services Administration (SAMSHA).[124] Also, over 1 million people misused prescription stimulants, about 1.5 million people misused tranquilizers and 271,000 people were first time sedative misusers, all within the past year.[124]

Gabapentinoids are emerging as a drug class of public health concern as they have come under public health scrutiny for their rising prescribing trends and their presence in fatalities due to medications, specifically opioid overdose. The gabapentin prescription rate in the United States increased from approximately 39 million in 2012 to 64 million in 2016.[14] According to a report on medicine use and spending in the United States, gabapentin prescriptions rose further to 67 million in 2018 making it the sixth highest prescribed medication in 2018.[15] This upward spike in recent years is noteworthy as gabapentin was approved for epilepsy and postherpetic neuralgia in 1993 and 2004, respectively,[113] and there are no recent FDA-approved indications for gabapentin that can justify or explain this rise. Similarly, the sales of pregabalin more than doubled to about $4.4 billion in 2016, from about $2 billion in 2012.[14]

Although the CDC recommends gabapentinoids as first-line agents for the treatment of neuropathic pain, this rise in their utilization cannot be explained by a concurrent increase in neuropathic pain diagnosis or newly approved indications. Thus, the significant increase in gabapentinoid use is presumed to be a response to the need for alternatives to opioids for pain management.[14]

2.4.5.2 Evidence and consequences of gabapentinoid misuse

Several studies in Europe indicating an increase in gabapentin and pregabalin use led to subsequent investigation of gabapentin and pregabalin abuse in Europe and beyond. A study investigating pregabalin abuse using the Swedish spontaneous adverse drug reaction reporting system was published in 2010. The results showed there was a rapid increase in pregabalin use within two years (9.3 million defined daily doses used in 2009, compared to 4.6 million defined daily doses in 2007) and in the likelihood of pregabalin to be abused. They also identified 16 cases indicative of pregabalin abuse out of 198 reports of drug abuse or addiction.[125, 126] A similar pharmacovigilance study published in 2016 using the French pharmacovigilance database identified 8 pregabalin cases out of 521 drug abuse or dependence cases between January 1, 2010 and December 31, 2015.[127] A study published in 2013 using the German Federal Institute for Drugs and Medical Devices identified fifty-five reports of pregabalin abuse and dependence between April 2008 and August 2012[12] Another study in Scotland, published in 2012 found that there were noticeable increases in gabapentin prescriptions since 2002 when it was approved for postherpetic neuralgia. They also found the presence of gabapentin in postmortem reports (48 out of 1,400 post-mortem reports included gabapentin).[128]

An analysis of the European Medicines Agency's EudraVigilance database between 2004 to 2015 showed that about 6.6% (7,639 out of 115,616) and 4.8% (4,301 out of 90,166) of reports regarding abuse, misuse or dependence were associated with pregabalin and gabapentin, respectively. They also discovered that 27 and 86 deaths were attributable to pregabalin and gabapentin, respectively, and most of these deaths occurred in cases with concomitant opioid use. Although this study evaluated reports over a twelve year span (2004-2015), about 67% percent of the pregabalin cases and 60% of the gabapentin cases they identified occurred within 3 years alone (2013-2015), which

indicates a sharp rise in those years compared to previous years.[129] The rise in gabapentinoid abuse-related events and deaths identified in recent years in the European pharmacovigilance database has also been identified in the United States. Evoy et al. analyzed the Food and Drug Administration Adverse Events Reporting System (FAERS) between 2012 to 2016.[59] They found that a larger percentage of the gabapentinoid abuse-related events and deaths occurred within the two most recent years of the study (2015-2016). Out of 10,038 gabapentin adverse events identified within 2012-2016, 5.7% (576 out of 10,038) were events specifically related to gabapentin abuse. Of these 576 abuse-related events, 66% (381 out of 576) occurred between 2015 and2016 alone. Also, 106 of these 576 abuse-related events led to fatalities, 66% (70 out of 106) of which occurred between 2015 and 2016. Within this time frame (2012 – 2016), 571 pregabalin adverse events were identified. Approximately 10% [10.2% (58 out of 571)] of these events were reports related to pregabalin abuse. Of these 58 abuse-related events, 60% (35 out of 58) occurred between 2015 and 2016. Out of the 58 abuse-related events, 24 fatalities were recorded, with 83% (20 out of 24) of these deaths in 2015 to 2016 alone.[59]

A study by Smith et al. (N = 33) conducted in Appalachian Kentucky, United States was used to characterize patterns and reasons for gabapentin misuse. They found that most patients were initiated on gabapentin for indications such as neuralgia, insomnia, depression, anxiety and opioid detoxification. Also, some respondents considered gabapentin more effective than opioids for their pain, cheaper than opioids, as well as helpful for coping with withdrawal symptoms from opioids. They also found that the respondents used specific doses to give them the "high" they wanted, but most of them preferred to take them with caffeine, because caffeine "makes them better."[130] These findings were consistent with a larger study (N = 503) conducted by the same group, also in Appalachian Kentucky.[131, 132] They found that about 15% of participants who reported

using prescription opioids for nonmedical use also used gabapentin “to get high”. Also, drug dealers were a major source of obtaining gabapentin (36%) while prescriptions written by physicians accounted for 52% of access to gabapentin within this cohort. In addition, gabapentin was reported to be available from drug dealers at a cost of less than $1 per pill.[131, 132]

Evoy et al. conducted a systematic review (N = 59 studies) on gabapentinoid abuse and concluded that there is an increasing trend in patients taking higher than prescribed doses to attain euphoria. They also found that the number of people who abused gabapentinoid in the general population was 1.6%, but prevalence of gabapentinoid abuse among those abusing opioids was higher, and ranged from 3% to 68% across different studies.[126]

Peckham et al. conducted the first large retrospective database study analyzing the prevalence and predictors of gabapentin abuse using the Truven Health MarketScan® commercial database.[25] The database contains medical and pharmacy claims for about 50 million people with commercial insurance, of which 840,000 were included in the study. They calculated Lorenz-1 curves to determine the proportion of consumption in the top 1% of users compared to the total population utilization. Gabapentin and pregabalin had Lorenz-1 values of 19% and 15%, respectively. This indicates the abuse potential of gabapentin and preagablin as they both met the standard 15% threshold value which is associated with high abuse potential.[25, 59] They also found that about 40% of gabapentin users and 39% of pregabalin users had concurrent opioid use for at least 120 days.[25] In a subsequent study, they found that 24% of patients who had both gabapentin and opioid prescriptions had no less than three pharmacy claims that exceeded recommended dosage limits, in contrast to 3% of patients on gabapentin only and 8% of patients on opioids only.[61]

Another retrospective database study was conducted by Pauly et al. using the IBM Marketscan® Commercial Claims and Encounters Database.[35] The database contains administrative claims for about 20 to 30 million enrollees annually. The study evaluated the trends in gabapentin prescription from 2009 to 2016. They found that the prevalence of gabapentin prescribing in 2009 was 13.3 recipients per 1,000 beneficiaries. However, by 2016, the prevalence had more than doubled to 27.1 recipients per 1,000 beneficiaries. They also found that gabapentin prescribing rates differed across the United States, with Kentucky having the highest rate of 43.9 recipients per 1000 beneficiaries and Washington DC. having the lowest rate of 12.7 recipients per 1000 beneficiaries.[35] A post-mortem study in five sites within the United States (Kentucky, Maricopa county in Arizona, North Carolina, Northeast Tennessee and West Virginia) found that gabapentin was implicated in an average of 22% of overdose-related deaths. This positive association of gabapentin with overdose deaths varied significantly across the different locations; Northeast Tennessee was the lowest (4%) while Kentucky was the highest (41%).[26]

Another study investigating gabapentin levels in post-mortem cases was conducted in West Virginia. They reviewed fatalities that occurred over 4 years (2014 to 2017) within the Western region of the Office of the Chief Medical Examiner in West Virginia and found 104 cases where gabapentin was present. The chief pathologist determined that gabapentin played a direct role in 49 fatalities and a contributory role either by toxicity or overdose in 11 other cases.[133]

There are currently no national estimates on mortality, morbidity, or economic losses due to gabapentinoid misuse in the United States. The studies evaluating gabapentinoid misuse and abuse have described some of the clinical effects of misuse and abuse, as well as the increased consequences when used concomitantly with opioids.[59, 126, 129, 130, 131] Some misusers of pregabalin have described a dose related effect when

pregabalin is misused. At 900mg, pregabalin misusers experience some euphoria, difficulty walking, drunken feeling and color altered vision. At 1200mg, euphoria and drowsiness is established and at doses greater than 1500mg, misusers experience hallucinations, increased euphoria, dissociation and anxiety.[134]

The concern about gabapentinoid misuse increases in patients who use opioids, as the risk of fatality from opioid overdose is increased. Research shows that there is a possible increase of up to 60% in opioid-associated deaths when doses of gabapentin greater than 900mg are used concurrently with opioids. This is because gabapentin misuse in combination with opioids can lead to a fourfold increase in the risk of respiratory depression.[61] In December 2019, the FDA issued warnings about the possibility of severe breathing problems in patients using gabapentin or pregabalin.[135] The agency also required that the labeling of gabapentinoids be updated with warnings on the risk of respiratory depression. In addition, the agency is requiring manufacturers to conduct clinical trials evaluating the abuse potential of gabapentinoids with focus on assessing their respiratory depressant effects.[135, 136]

Gabapentinoid misuse has been identified and defined in different ways: self-report of participants in prospective research,[130, 131] presence of gabapentinoids in toxicology reports[26, 128, 133, 137] analysis of pharmacovigilance database[12, 59, 125, 127, 129] and consistent overdose identified through prescription claims.[61, 25, 111] Due to the nature of this study (i.e., secondary database analysis) and to aid comparison with similar studies,[111, 59] misuse will be defined as three or more pharmacy claims exceeding a daily dose threshold of 3600mg for gabapentin and 600mg for pregabalin.

There is evidence to show that gabapentinoid misuse and abuse is becoming a significant concern within the United States and beyond. The increase in drug overdose cases and fatalities involving gabapentinoids has attracted notable research interest. The

misuse and abuse potential of gabapentinoids is an emerging research area, and as such, there are gaps in describing the effects and consequences of gabapentinoid misuse across different population groups. One such gap is the absence of investigation into gabapentinoid misuse among Medicaid recipients.

2.4.5.3 Factors associated with gabapentinoid misuse

Factors contributing to increased gabapentinoid misuse include: easier access to gabapentinoid prescriptions, lower costs than opioids, limited prescriber knowledge regarding abuse potential, non-classification of gabapentin as a controlled substance, and prevalent use for off-label conditions.[126, 60,118,131]

The risk for gabapentinoid misuse is also increased in patients with previous or concurrent opioid use or abuse.[126,118] When gabapentinoids are used in combination with opioids, they may potentiate the euphoric effect of opioids, which can lead to opioid users seeking and using higher than prescribed doses of gabapentinoids. Some studies show that overdose of gabapentinoids alone may not have lethal effects but when used in addition to opioids and sedatives, they can lead to respiratory depression and opioid-associated fatality.[138, 60] A case control study evaluating opioid users in Canada found that about 46% of gabapentin users had at least one concurrent opioid prescription, and this concomitant use of gabapentin and opioids increased the risk of opioid related fatality by 49%.[107]

The post-mortem study conducted in Scotland found that 75% of cases (36 out of 48) with gabapentin in their toxicology report also had morphine and/or methadone on their report.[128] Similarly, Peckham et al. in their analysis of the Truven Health MarketScan® database found that only 2% of patients on gabapentin without opioids met their criteria for prolonged overuse, while 11% of patients on gabapentin and opioids were in the prolonged overuse category. They also found that predictors or risk factors for misuse

differed between the two groups: the gabapentin-only group having insomnia, euphoria and bipolar disorder as the top three predictors, while the gabapentinoid and opioid group had detoxification, altered mental state and addiction as their top three risk factors.[111]

Another toxicology study examining the prevalence of gabapentin in impaired driving cases, found only about 7% of gabapentin positive cases had just gabapentin in their blood samples, while the remaining 93% of gabapentin positive cases had other psychoactive drugs in their sample. Benzodiazepines were found in 44%, opioids in 43%, antidepressants in 43%, other CNS depressants in 36%, antiepileptic drugs in 25%, cannabinoids in 15%, stimulants in 11% and ethanol in 6% of these polysubstance cases.[137] This indicates that the probability of misusing gabapentinoids is higher when there is opioid or polysubstance use. A post-mortem study in West Virginia also found that 77.6% (38 out of 49) of cases where gabapentin was a direct cause of death also had at least one opiate present in their toxicology report.[133]

It is not clear if gender plays a role in increased risk of gabapentinoid misuse and abuse, as the distributions of misuse and abuse between males and females have been inconsistent across studies.[12,26,129] Also, the role of age in gabapentinoid misuse and abuse has not been established but abuse-related events have been observed more in younger than older participants. [59, 133]

2.4.5.4 Policies and efforts to address gabapentinoid misuse

In the United Kingdom, both gabapentin and pregabalin were classified as class C controlled substances starting on April 1, 2019. This classification will ensure that prescribers sign their prescriptions by hand and that they are dispensed within 28 days from the prescription date.[139]

However, in the United States, only pregabalin is recognized as a schedule V controlled substance while gabapentin remains unclassified as a controlled substance at the federal level. This has given rise to various state-level legislations, regulations and monitoring efforts to address the increasing evidence of gabapentin misuse.

Kentucky was the first state (effective July 2017) to classify gabapentin as a schedule V controlled substance. This reclassification was established in response to the presence of gabapentin in 93 out of 407 (22.9%) cases of overdose-related deaths in Jefferson county alone, and in about one-third of all drug related deaths across Kentucky in 2016. Schedule V restricts prescribing gabapentin to only prescribers registered with the DEA, thereby limiting the ability of mid-level providers to prescribe gabapentin. Also, in line with the DEA requirement for schedule III and IV medication refills, no more than a 6-month supply (i.e., maximum of 5 refills) of gabapentin can be authorized at a time.[60, 27, 28]

West Virginia placed gabapentin on its schedule V controlled drugs list effective June 7, 2018 with Tennessee following closely after on July 1, 2018. Michigan and Virginia also reclassified gabapentin to a schedule V medication, effective January 2019 and July 2019, respectively.[30, 31, 32] Similarly, North Dakota and Alabama reclassified gabapentin to a schedule V medication, effective April 2019 and November 2019, respectively.[33, 34] Other states such as Minnesota, Ohio, Wyoming, Massachusetts, Nebraska, New Jersey, Kansas and New York have included gabapentin in their prescription drug monitoring programs (PDMPs) (Table 2.4).[60, 140]

Table 2.4: Regulatory action to address gabapentin by various states[60,33, 34, 140, 141]

State	Action	Date
Kentucky	Schedule V reclassification	July 1, 2017
West Virginia	Schedule V reclassification	June 7, 2018
Tennessee	Schedule V reclassification	July 1, 2018
Michigan	Schedule V reclassification	January 1, 2019
North Dakota	Schedule V reclassification	April 10, 2019
Virginia	Schedule V reclassification	July 1, 2019
Alabama	Schedule V reclassification	November 18, 2019
Minnesota	PDMP reporting[1]	August 1, 2016
Ohio	PDMP reporting	December 1, 2016
Wyoming	PDMP reporting	May 17, 2017
Massachusetts	PDMP reporting	August 1, 2017
Nebraska	PDMP reporting	January 1, 2018
New Jersey	PDMP reporting	May 7, 2018
Kansas	PDMP reporting	July 25, 2018
New York	PDMP reporting	January 1, 2019

[1] Prescription drug monitoring programs PDMPs use electronic databases to monitor and report prescription information for controlled substances.

2. 5 STUDY SIGNIFICANCE

The increasing identification of both gabapentin and pregabalin as medications of potential misuse and abuse has given rise to public health scrutiny and debate. However, limited studies have been conducted to evaluate the prevalence of their misuse alone or

concurrently with opioids, as well as their subsequent clinical and economic burden across the United States. Evaluating gabapentinoid misuse is important as the opioid epidemic is one of the largest health concerns in the country**.** Gabapentinoids have been considered safer alternatives to reduce opioid overuse and subsequent misuse and abuse. However, research shows that concurrent use of gabapentinoids with opioids increase the risk of overdose and fatalities.

To the author's knowledge, only commercial insurance prescription databases in the United States have been studied (i.e., the Truven Health MarketScan® and the IBM Marketscan® databases). However, Medicaid and Medicare recipients were excluded because of the nature of these databases, which precludes information about this patient population. Texas is one of the states where, as of 2020, gabapentin has not been reclassified or placed on a PDMP. In addition, to date, Texas has not reported data on the prevalence of gabapentinoid misuse in the state. Hence, the purpose of this study is to evaluate the prevalence and factors associated with gabapentinoid use and misuse using the Texas Medicaid database.

Chapter 3: Methodology

3.1 Chapter overview

Prevalence is the term used to describe the proportion of a specific population affected by a disease or condition of interest within a period. It is obtained by comparing the affected people to the total number of people studied. It can be expressed as a fraction, a percentage or the number of cases per 10,000 or 100,000 people.[142] This study examined the prevalence of gabapentinoid misuse among Texas Medicaid gabapentinoid users, as well as clinical and demographic factors that may be related to misuse. This chapter discusses institutional review board approval, study objectives and hypotheses, study design and data source, study variables, statistical analytical methods and potential limitations.

3.2 Institutional review board approval

This study was reviewed by the Institutional Review Board (IRB) of The University of Texas at Austin. It was determined that this project does not require IRB oversight because it was conducted with a de-identified data set; hence, there are no direct links to patient identifiers.

3.3 Study objectives and hypotheses

1. To quantify the proportion of Texas Medicaid gabapentinoid users with gabapentinoid misuse.

2. To describe and compare the demographic characteristics (age and gender) of Texas Medicaid gabapentinoid users misusing gabapentinoids versus gabapentinoid users not misusing gabapentinoids.

   Ho_{2a}: There is no significant difference in age among gabapentinoid users misusing gabapentinoids versus gabapentinoid users not misusing gabapentinoids.

   Ho_{2b}: There is no significant difference in gender among gabapentinoid users misusing gabapentinoids versus gabapentinoid users not misusing gabapentinoids.

3. To determine if gabapentinoid misuse differs between gabapentinoid users with and without neuropathic pain.

   Ho_3: There is no significant difference in the proportion of patients with gabapentinoid misuse among gabapentinoid users with and without neuropathic pain.

4. To determine if gabapentinoid misuse differs based on gabapentinoid type.

   H_4: The proportion of patients with gabapentinoid misuse is significantly higher in gabapentin users compared to pregabalin users.

5. To determine if gabapentinoid misuse differs between concurrent opioid users and non-concurrent opioid users.

   H_5: The proportion of patients with gabapentinoid misuse is significantly higher in concurrent opioid users compared to non-concurrent opioid users.

6. To determine the relationship between likelihood of gabapentinoid misuse by age, gender, neuropathic pain diagnosis, gabapentinoid type and concurrent opioid use.

   Ho_{6a}: There is no significant relationship between the likelihood of patients misusing gabapentinoids and age, while controlling for covariates.

   Ho_{6b}: There is no significant relationship between the likelihood of patients misusing gabapentinoids and gender, while controlling for covariates.

   Ho_{6c}: There is no significant relationship between the likelihood of gabapentinoids users misusing gabapentinoid and neuropathic pain diagnosis status, while controlling for covariates.

   H_{6d}: Gabapentin users are significantly more likely to misuse gabapentinoids than pregabalin users, while controlling for covariates.

   H_{6e}: Concurrent opioid users are significantly more likely to misuse gabapentinoids than non-concurrent opioid users, while controlling for covariates.

3.4 STUDY DESIGN AND DATA SOURCE

This study is a retrospective database analysis using Texas Medicaid prescription and medical claims data for the period between January 1, 2012 to August 30, 2016. The study subjects were adults aged 18 to 63 with at least one gabapentinoid (gabapentin or pregabalin) prescription.

3.4.1 Inclusion criteria

Texas Medicaid patients who met the following criteria were included:

1. Between the ages of 18 and 63 at the index date;

2. Continuous enrollment for at least 6 months pre-index and 12 months post-index;

3. At least one prescription for gabapentin or pregabalin.

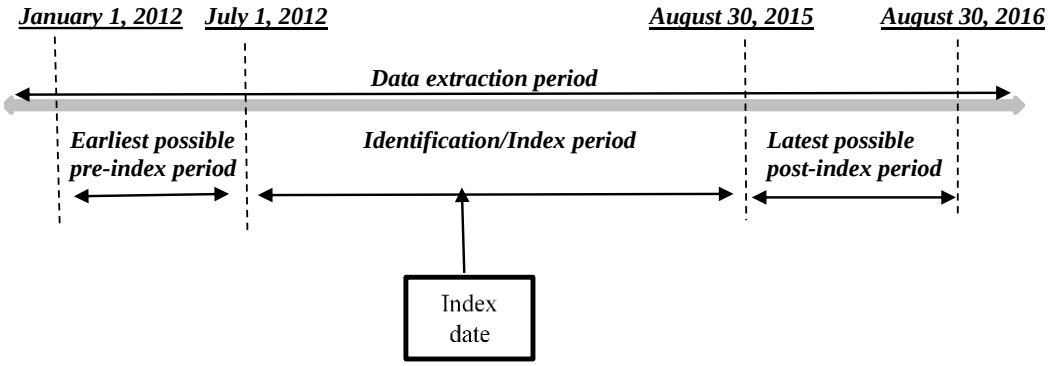
3.4.2 Index date

The index date was the date of the first prescription claim for a gabapentinoid (gabapentin or pregabalin) without any previous claims 6 months prior.

3.4.3 Data collection and study periods

The following data were obtained from the Texas Medicaid eligibility, medical and prescription claims database: de-identified patient identification number, gender, age, diagnosis codes (ICD-9-CM and ICD-10-CM codes), prescription medication name and type identifiers (i.e., National Drug Codes [NDCs], American Hospital Formulary Service [AHFS] code and Generic Code Sequencing Number [GCN_Seq No]), prescription fill date, quantity supplied, days' supply and prescriber type. Data from Texas Medicaid were extracted from January 1, 2012 to August 30, 2016. Subjects included in the study were identified based on the presence of a prescription claim for a gabapentinoid during the index period (July 1, 2012 to August 30, 2015) (Figure 3.1).

Figure 3.1: Data extraction and subject identification periods



3.5 STUDY VARIABLES

This section describes the study variables and operational definition of each variable (Table 3.1).

3.5.1 Dependent variable

The dependent variable in this study was gabapentinoid misuse (Table 3.1). This was determined by calculating daily dosage during the 12-month post-index period using pharmacy claims. For each claim, total supply dispensed in milligrams was calculated by multiplying quantity supplied by strength prescribed. Daily dosage was then calculated using total supply dispensed in milligrams divided by days' supply. Misuse was defined as the presence of three or more claims exceeding the daily dose threshold of 3600mg for gabapentin and 600mg for pregabalin.

Total supply = Quantity supplied x strength prescribed

Daily dose = Total supply dispensed in milligrams / days' supply

3.5.2 Independent variable

The independent variables included sociodemographic characteristics (age, gender), and clinical characteristics (concurrent opioid use, neuropathic pain diagnoses and gabapentinoid type). Concurrent opioid use was defined as having a pharmacy claim for at least 90 days' supply of opioid concurrently with a gabapentinoid during the 12-month post-index period. Gabapentinoid type was either gabapentin or pregabalin, which was assigned based on the index prescription; thus, an intent-to-treat approach was used. See Table 3.1 for operational definitions of the independent variables. Neuropathic pain diagnoses were identified using ICD-9-CM and ICD-10-CM diagnostic codes (Table 3.2).

Table 3.1: Study variables and operational definitions

STUDY VARIABLES	OPERATIONAL DEFINITION
DEPENDENT VARIABLE	
Gabapentinoid misuse	Three or more claims exceeding daily dose threshold of 3600mg for gabapentin or 600mg for pregabalin during the 12-month post-index period (see Table 3.3 for brand/generic names of gabapentin and pregabalin on the Texas Medicaid formulary). [0 = no misuse; 1 = misuse]
INDEPENDENT VARIABLE	
Neuropathic pain diagnosis	Neuropathic pain diagnoses including postherpetic neuralgia; diabetes with neurological manifestations (diabetic neuropathy); and others (nerve root and plexus disorders; mononeuritis of upper limb and mononeuritis multiplex; mononeuritis of lower limb and unspecified site; hereditary and idiopathic peripheral neuropathy; inflammatory and toxic neuropathy) identified using ICD-9-CM and ICD-10-CM diagnostic codes. (see Table 3.2 for ICD codes) [0 = no neuropathic pain present (excluding any of the above); 1 = neuropathic pain present (including any of the above)]
Gabapentinoid type	Specific type of index gabapentinoid used [1 = Gabapentin; 2 = Pregabalin]
Concurrent opioid use	Patients with pharmacy claims for at least 90 days' supply of opioid concurrently with a gabapentinoid during the 12-month post-index period (see Table 3.3 for brand/generic names of opioids on the Texas Medicaid formulary). [0 = non-concurrent opioid use; 1 = concurrent opioid use]
Socio-demographic factors	**Age:** Continuous variable, measured as age of subject at index date Categorical variable [18-24; 25-40; 41-63] **Gender:** Categorical variable [0 = male, 1 = female]

Table 3.2: ICD-9-CM and ICD-10-CM diagnostic codes for neuropathic pain[143]

	Diagnostic conditions	ICD-9-codes	ICD-10 codes
Postherpetic neuralgia	Herpes zoster with unspecified nervous system complications	053.10	B02.29
	Geniculate herpes zoster	053.11	B02.21
	Postherpetic trigeminal neuralgia	053.12	B02.22
	Postherpetic polyneuropathy	053.13	B02.23
	Herpes zoster myelitis	053.14	B02.24
	Herpes zoster with other nervous system complications	053.19	B02.29
	Herpes zoster with unspecified complications	053.8	B02.8
Diabetes with neurological manifestations (Diabetic neuropathy)	Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled	250.60	E11.40
	Diabetes with neurological manifestations, type I [juvenile type], not stated as uncontrolled	250.61	E10.40
	Diabetes with neurological manifestations, type II or unspecified type, uncontrolled	250.62	E11.40 with E11.65
	Diabetes with neurological manifestations, type I [juvenile type], uncontrolled	250.63	E10.40 with E10.65
Nerve, nerve root and plexus disorders	Trigeminal neuralgia	350.1	G50.0
	Atypical facial pain	350.2	G50.1
	Other disorders of trigeminal nerve	350.8	G50.8
	Disorder of trigeminal nerve, unspecified	350.9	G50.9
	Bell's palsy	351.0	G51.0
	Geniculate ganglionitis	351.1	G51.1
	Melkersson's syndrome	351.8	G51.2
	Clonic hemifacial spasm	351.8	G51.31 -G51.39
	Facial myokymia	351.8	G51.4
	Other disorders of facial nerve	351.8	G51.8

Table 3.2: ICD-9-CM and ICD-10-CM diagnostic codes for neuropathic pain continued

	Disorder of facial nerve, unspecified	351.9	G51.9
	Disorders of olfactory nerve	352.0	G52.0
	Disorders of glossopharyngeal nerve	352.1 or 352.2	G52.1
	Disorders of vagus nerve	352.3	G52.2
	Disorders of hypoglossal nerve	352.5	G52.3
	Disorders of multiple cranial nerves	352.6	G52.7
	Disorders of other specified cranial nerves	352.4	G52.8
	Cranial nerve disorder, unspecified	352.9	G52.9 or G53
	Brachial plexus lesions/disorders	353.0	G54.0
	Lumbosacral plexus lesions/disorders	353.1	G54.1
	Cervical root lesions/disorders, not elsewhere classified.	353.2	G54.2
	Thoracic root lesions/disorders, not elsewhere classified	353.3	G54.3
	Lumbosacral root lesions/disorders, not elsewhere classified	353.4	G54.4
	Neuralgic amyotrophy	353.5	G54.5
	Phantom limb (syndrome)	353.6	G54.6 or G54.7
	Other nerve root and plexus disorders	353.8	G54.8 or G55
	Unspecified nerve root and plexus disorder	353.9	G54.9
	Carpal tunnel Syndrome	354.0	G56.00- 56.03
	Other lesion of median nerve	354.1	G56.10-56.13
	Lesion of the ulnar nerve	354.2	G56.20-56.23
	Lesion of the radial nerve	354.3	G56.30-56.33
	Causalgia of upper limb	354.4	G56.40-56.43
	Mononeuritis multiplex	354.5	G58.7

Table 3.2: ICD-9-CM and ICD-10-CM diagnostic codes for neuropathic pain continued

	Other mononeuritis of upper limb	354.8	G56.80-56.83; G58.0
	Mononeuritis of upper limb, unspecified	354.9	G56.90-56.93
	Lesion of sciatic nerve	355.0	G57.00-57.03
	Meralgia paresthetica	355.1	G57.10- 57.13
	Other lesion of femoral nerve	355.2	G57.20-57.23
	Lesion of lateral popliteal nerve	355.3	G57.30-57.33
	Lesion of medial popliteal nerve	355.4	G57.40-57.43
	Tarsal tunnel syndrome	355.5	G57.50-57.53
	Lesion of plantar nerve	355.6	G57.60-57.63
	Causalgia of lower limb	355.71	G57.70-57.73
	Other mononeuritis of lower limb	355.79	G57.80-57.83
	Mononeuritis of lower limb unspecified	355.8	G57.90-57.93
	Mononeuritis of unspecified site	355.9	G58.8, G58.9 or G59
Polyneuropathies and other disorders of the peripheral nervous system. Inflammatory and toxic neuropathy	Hereditary peripheral neuropathy	356.0	G60.0 or G60.2
	Peroneal muscular atrophy	356.1	G60.0
	Hereditary sensory neuropathy	356.2	G60.0
	Refsum's disease	356.3	G60.1
	Idiopathic progressive polyneuropathy	356.4	G60.3
	Other specified idiopathic peripheral neuropathy	356.8	G60.8
	Unspecified hereditary and idiopathic peripheral neuropathy.	356.9	G60.9
	Acute infective polyneuritis	357.0	G61.0
	Polyneuropathy in collagen vascular disease	357.1	G63

Table 3.2: ICD-9-CM and ICD-10-CM diagnostic codes for neuropathic pain continued

	Polyneuropathy in diabetes	357.2	E08.42 or E09.42 or E10.42 or E11.42 or E13.42
	Polyneuropathy in malignant disease	357.3	G63
	Polyneuropathy in other diseases classified elsewhere	357.4	G65.0 or G65.1 or G65.2
	Alcoholic polyneuropathy	357.5	G62.1
	Polyneuropathy due to drugs	357.6	G62.0
	Polyneuropathy due to other toxic agents	357.7	G61.1 or G62.2
	Chronic inflammatory demyelinating polyneuritis	357.81	G61.81
	Critical illness polyneuropathy	357.82	G62.81
	Other inflammatory and toxic neuropathy	357.89	G61.82, G61.89 or G64
	Unspecified inflammatory and toxic neuropathy	357.9	G61.9
	Radiation-induced polyneuropathy	357.7	G62.82
	Other specified polyneuropathies	357.89	G62.89
	Polyneuropathy, unspecified	357.9	G62.9
	Polyneuropathy in other diseases classified elsewhere	357.4	G63
	Sequelae of Guillain-Barré syndrome	357.4	G65.0
	Sequelae of other inflammatory polyneuropathy	357.4	G65.1
	Sequelae of toxic polyneuropathy	357.4	G65.2

Table 3.3: Brand/trade names of gabapentinoid and opioid medications on the Texas Medicaid formulary[144]

Drug Class	Generic name	Brand/Trade name
Gabapentinoid	Gabapentin	Gralise®, Gralise ER® Horizant ER®, Neurontin®
	Pregabalin	Lyrica®, Lyrica CR®
Opioids	Morphine, Morphine ER	Embeda ER®, Kadian ER®, Morphabond ER®, MS Contin ER®
	Oxycodone, Oxycodone ER, Oxycodone-Acetaminophen, Oxycodone-Aspirin, Oxycodone-Ibuprofen,	Endocet®, Nalocet®, Oxycontin®, Percocet®, Roxicodone®, Xtampza ER®
	Oxymorphone, Oxymorphone ER	Opana®
	Hydrocodone, Hydrocodone-Acetaminophen, Hydrocodone-Ibuprofen	Hysingla ER®, Ibudone®, Lorcet®, Norco®, Vicodin®
	Hydromorphone, Hydromorphone ER	Exalgo ER®, Dilaudid®,
	Fentanyl	Duragesic®, Actiq®, Fentora®, Lazanda®, Subsys®
	Methadone	Dolophine®, Methadose®
	Meperidine	Demerol®
	Buprenorphine, Buprenorphine-Naloxone	Belbuca®, Butrans®, Bunavail®, Suboxone®, Zubsolv®
	Butorphanol	
	Pentazocine, Pentazocine-Naloxone	
	Codeine, Acetaminophen-Codeine #2, Acetaminophen-Codeine #3, Acetaminophen-Codeine #4, Butalbital- Caffeine-Acetaminophen-Codeine, Butalbital- Aspirin-Caffeine-Codeine, Carisoprodol-Aspirin-Codeine	Ascomp with codeine®, Fiorinal-Codeine®, Tylenol with Codeine #3®, Tylenol with Codeine #4®
	Tramadol, Tramadol ER, Tramadol-Acetaminophen	Ultracet®, Ultram®
	Tapentadol	Nucynta®, Nucynta ER®

3.6 STATISTICAL ANALYSIS

SAS for windows, version 9.4 (SAS Institute, Cary NC) was used for all data analyses. All statistical analyses were conducted with two-tailed tests and a significance level of $p < 0.05$.

Objective 1 was addressed using frequencies. Objective 2 included descriptive and inferential analyses. Age was described using mean, standard deviation and range, while age categories and gender were described using frequencies. The inferential portion of Objective 2 was conducted using an independent samples t-test for the continuous age variable, while a chi-square test was conducted for age categories and gender. Chi-square tests were also used to analyze Objectives 3, 4 and 5. Objective 6 was analyzed using logistic regression.

3.6.1 Statistical test assumptions and sample size calculations

This section presents the test assumptions and sample size calculations for objectives that require statistical tests. A summary of sample size results is shown in Table 3.4 and a summary of the hypotheses and tests for each objective is included in Table 3.5.

3.6.1.1 Independent samples t-test

A t-test was used to test for differences in age (continuous) between the misuse and no misuse groups. The assumptions for the t-test include: 1) normal distribution of data; 2) homogeneity of variance; and 3) independence of observations.[145] The required sample size was calculated using G*Power software with medium effect size (d = 0.50), alpha level of 0.05 and power of 0.80 for a two-tailed t-test. The minimum required sample size for each group was 64, resulting in a total of 128.

3.6.1.2 Chi-square test

Chi-square tests were used to determine if there were differences in proportions among categorical variables. For this study, chi-square tests were used to assess differences in misuse with respect to: gender (Objective 2); patients with and without a neuropathic pain diagnosis (Objective 3); gabapentinoid type (Objective 4); concurrent opioid users and non-concurrent opioid users (Objective 5).

Assumptions required for the Chi-square test include: 1) nominal or categorical variables; 2) mutual exclusivity of variables; 3) independence of observations; and 4) at least 80% of the cells should contain a minimum expected frequency of 5 observations.[146] Sample size was calculated using G*Power software with medium effect size (f = 0.30), alpha level of 0.05 and power of 0.80. The minimum required sample size to use the chi-square test in this study was 88.

3.6.1.3 Logistic regression analysis

Logistic regression analysis was used to address Objective 6 because the dependent variable (gabapentinoid misuse) is binary (i.e., yes or no). The following is the logistic regression model that was used:

$$\ln [\pi(x)/(1-\pi(x))] = \beta0 + \beta1x1 + \beta2x2 + \beta3x3 + \beta4x4 + \beta5x5$$

$\pi(x)$ = probability of misusing gabapentinoids

$1-\pi(x)$ = probability of not misusing gabapentinoids

$\beta0$ = constant = intercept of the logistic regression model

x1 = age

x2 = gender

x3 = neuropathic pain diagnosis

x4 = gabapentinoid type

x5 = concurrent opioid use

Using G*Power software, the minimum sample size required was 1,168 (odds ratio = 1.2, Pr (Y=1/X=1) H_0 = 0.2, α = 0.05, power = 0.8). The logistic regression analysis required the largest sample size. Therefore a minimum sample size of 1,168 is necessary for this study.

Table 3.4: Minimum required sample size for each statistical test

Statistical test	**Independent samples t-test**	**Chi-square test**	**Logistic regression**
Minimum required sample size	126	88	1,168

Table 3.5: Summary of objectives, hypothesis, variables and statistical tests

Objective	Hypotheses	Dependent variable	Independent variable	Statistical procedure
1. To quantify the proportion of Texas Medicaid gabapentinoid users with gabapentinoid misuse.	N/A	Gabapentinoid misuse (Categorical Variable) [0 = no misuse, 1 = misuse]		Frequencies
2. To describe and compare the demographic characteristics (age and gender) of Texas Medicaid gabapentinoid users misusing gabapentinoids versus gabapentinoid users not misusing gabapentinoids.	N/A	Gabapentinoid misuse (Categorical Variable) [0 = no misuse, 1 = misuse]	Age (Continuous variable)	Mean, standard deviation, range
			Age (Categorical variable) [18-24; 25-40; 41-63]	Frequencies
			Gender (Categorical variable) [0 = male, 1 = female]	Frequencies
	Ho_{2a}: There is no significant difference in age among gabapentinoid users misusing gabapentinoids versus gabapentinoid users not misusing gabapentinoids.	Age (Continuous variable)	Gabapentinoid misuse (Categorical Variable) [0 = no misuse, 1 = misuse]	T-test
	Ho_{2b}: There is no significant difference in gender among gabapentinoid users misusing gabapentinoids versus gabapentinoid users not misusing gabapentinoids.	Gabapentinoid misuse (Categorical Variable) [0 = no misuse, 1 = misuse]	Gender (Categorical variable) [0 = male, 1 = female]	Chi-square test

Table 3.5: Summary of objectives, hypothesis, variables and statistical tests continued

3. To determine if gabapentinoid misuse differs between gabapentinoid users with and without neuropathic pain.	**Ho_3**: There is no significant difference in the proportion of patients with gabapentinoid misuse among gabapentinoid users with and without neuropathic pain.	Gabapentinoid misuse (Categorical Variable) [0 = no misuse, 1 = misuse]	Neuropathic pain diagnosis [0 = no neuropathic pain; 1 = neuropathic pain]	Chi-square test
4. To determine if gabapentinoid misuse differs based gabapentinoid type.	**H_4:** The proportion of patients with gabapentinoid misuse is significantly higher in gabapentin users compared to pregabalin users.	Gabapentinoid misuse (Categorical Variable) [0 = no misuse, 1 = misuse]	Gabapentinoid type [1 = gabapentin; 2 = pregabalin]	Chi-square test
5. To determine if gabapentinoid misuse differs between concurrent opioid users and non-concurrent opioid users.	**H_5**: The proportion of patients with gabapentinoid misuse is significantly higher in concurrent opioid users compared to non-concurrent opioid users.	Gabapentinoid misuse (Categorical Variable) [0 = no misuse, 1 = misuse]	Opioid use [0 = non-concurrent opioid use; 1 = concurrent opioid use]	Chi-square test
6. To determine the relationships between likelihood of gabapentinoid misuse and age, gender, neuropathic pain diagnosis, gabapentinoid type and concurrent opioid use.	**Ho_{6a}:** There is no significant relationship between the likelihood of patients misusing gabapentinoids and age, while controlling for covariates*	Gabapentinoid misuse (Binary Variable) [0 = no misuse, 1 = misuse]	Age (Continuous variable)	Logistic regression analysis
	Ho_{6b}: There is no significant relationship between the likelihood of patients misusing gabapentinoids and gender, while controlling for covariates *	Gabapentinoid misuse (Binary Variable) [0 = no misuse, 1 = misuse]	Gender (Categorical variable) [0 = male, 1 = female]	Logistic regression analysis

Table 3.5: Summary of objectives, hypothesis, variables and statistical tests continued

	Ho_{6c}: There is no significant relationship between the likelihood of gabapentinoid users misusing gabapentinoids and neuropathic pain diagnosis status, while controlling for covariates. *	Gabapentinoid misuse (Binary Variable) [0 = no misuse, 1 = misuse]	Neuropathic pain diagnosis [0 = no neuropathic pain; 1 = neuropathic pain]	Logistic regression analysis
	H_{6d}: Gabapentin users are significantly more likely to misuse gabapentinoids than pregabalin users, while controlling for covariates.*	Gabapentinoid misuse (Binary Variable) [0 = no misuse, 1 = misuse]	Specific type of index gabapentinoid used. [1 = Gabapentin; 2 = Pregabalin]	Logistic regression analysis
	H_{6e}: Concurrent opioid users are significantly more likely to misuse gabapentinoids than non-concurrent opioid users, while controlling for covariates.*	Gabapentinoid misuse (Binary Variable) [0 = no misuse, 1 = misuse]	Opioid use. [0 = non-concurrent opioid use; 1 = concurrent opioid use]	Logistic regression analysis

*Covariates: age, gender, neuropathic pain diagnosis, gabapentinoid type and concurrent opioid use

Chapter 4: Results

4.1 CHAPTER OVERVIEW

This chapter describes the study results. First, the extraction process of patient selection from the database will be presented, followed by the results for each study objective.

4.2 FINAL SAMPLE

The initial population consisted of 149,023 patients with at least one gabapentinoid prescription during the study period (July 1, 2012 – August 30, 2015). After applying all inclusion and exclusion criteria, there were 39,000 eligible patients for the final sample (Table 4.1).

Table 4.1: Attrition of study subjects

Criteria	**Subjects excluded**		**Subjects remaining**	
	N	**%**	**N**	**%**
Initial population (patients with at least one gabapentinoid prescription between July 1, 2012 and August 30, 2015			149,023	100
Excluded if had index date prior to July 1, 2012 or after August 30, 2015	62,732	42.1	86,291	57.9
Sample after prior stage			**86,291**	**100**
Included age 18 to 63 at index date	7,487	8.7	78,804	91.3
Sample after prior stage			**78,804**	**100**
Included if continuous enrollment (patients with claims for at least 6 quarters during the study period)	39,804	50.5	39,000	49.5
Final sample (total patients excluded or remaining from initial sample)	**110,023**	**73.8**	**39,000**	**26.2**

4.3 STUDY OBJECTIVES

4.3.1 Objective 1: To quantify the proportion of Texas Medicaid gabapentinoid users with gabapentinoid misuse.

Objective 1 was to quantify the proportion of Texas Medicaid gabapentinoid users with gabapentinoid misuse. There were N = 81 (0.2%) gabapentinoid users who met the criteria for gabapentinoid misuse (Table 4.2).

Table 4.2: Proportion of gabapentinoid users with gabapentinoid misuse (N=39,000)

	N	%
Misuse	81	0.2
No misuse	38,919	99.8
Total	39,000	100.0

4.3.2 Objective 2: To describe and compare the demographic characteristics (age and gender) of Texas Medicaid gabapentinoid users misusing gabapentinoids versus gabapentinoid users not misusing gabapentinoids.

Objective 2 was to compare the demographic (age and gender) characteristics of gabapentinoid misusers with non-misusers (Table 4.3). Note that race/ethnicity was omitted due to missing values. Overall, the majority of gabapentinoid users were 41 to 63 years of age (76.4%) with a mean±SD age of 48.2±10.7 years and they were predominantly female (68.1%).

When comparing gabapentinoid misusers to non-misusers, a t-test revealed that gabapentinoid misusers were significantly younger than gabapentinoid non-misusers (45.1±11.0 vs. 48.2±10.7, respectively; p = 0.0084). Among the age groups, a chi-square

test revealed that there was no significant difference in the proportion of misusers across three age group categories, 18-24, 25-40, and 41-63, respectively ($X^2 = 4.2$, p =0.1219). Therefore, the hypothesis below was rejected. Note that although both t-test and chi-square tests were run for age, the t-test was associated with the hypothesis below.

*Ho_{2a}**: There is no significant difference in age among gabapentinoid users misusing gabapentinoids versus gabapentinoid users not misusing gabapentinoids.* ***Rejected***

With respect to gender, a chi-square test revealed that a significantly ($X^2 = 7.0$, p = 0.0079) higher proportion of males (0.3%) misused gabapentinoids compared to females (0.2%). Therefore, the hypothesis below was rejected.

Ho_{2b}: There is no significant difference in gender among gabapentinoid users misusing gabapentinoids versus gabapentinoid users not misusing gabapentinoids. ***Rejected***

Table 4.3: T-test and chi-square comparison of demographic characteristics of gabapentinoid users (N = 39,000)

Demographic characteristics	**All users N (col %)**	**Misuse N (row %)**	**No misuse N (row %)**	**p-value**
Age				
Mean (±SD)	48.2 (±10.7)	45.1 (±11.0)	48.2 (±10.7)	0.0084[a]
Age groups, N (%)				
18-24	1,126 (2.9%)	5 (0.4%)	1,121 (99.6%)	0.1219[b]
25-40	8,083 (20.7%)	20 (0.3%)	8,063 (99.7%)	
41-63	29,791 (76.4%)	56 (0.2%)	29,735 (99.8%)	
Total	39,000 (100.0%)	81 (0.2%)	38,919 (99.8%)	

4.3: T-test and chi-square comparison of demographic characteristics of gabapentinoid users (N = 39,000) continued

Gender, N (%)				
Females	26,543 (68.1%)	44 (0.2%)	26,499 (99.8%)	0.0079[b]
Males	12,457 (31.9%)	37 (0.3%)	12,420 (99.7%)	
Total	39,000 (100.0%)	81 (0.2%)	38,919 (99.8%)	

[a] T-test [b]Chi-square test

4.3.3 Objective 3: To determine if gabapentinoid misuse differs between gabapentinoid users with and without neuropathic pain.

Objective 3 was to determine if gabapentinoid misuse differs between gabapentinoid users with and without neuropathic pain (Table 4.4). Overall, slightly over one-half (51.9%; N=20,247) of the subjects had a neuropathic pain diagnosis.

A chi-square test revealed that gabapentinoid misuse was significantly ($X^2 = 7.0$, p = 0.0078) higher among gabapentinoid users with neuropathic pain (0.3%) compared to gabapentinoid users without neuropathic pain (0.1%). Therefore, the hypothesis below was rejected.

Ho_3: There is no significant difference in the proportion of patients with gabapentinoid misuse among gabapentinoid users with and without neuropathic pain. ***Rejected***

Table 4.4: Chi-square comparison of gabapentinoid misuse between users with and without neuropathic pain (N = 39,000)

Diagnosis	All users N (col %)	Misuse N (row %)	No misuse N (row %)	p-value
Neuropathic pain	20,247 (51.9%)	54 (0.3%)	20,193 (99.7%)	0.0078[a]
No neuropathic pain	18,753 (48.1%)	27 (0.1%)	18,726 (99.9%)	
Total	39,000 (100.0%)	81 (0.2%)	38,919 (99.8%)	

[a] Chi-square test

4.3.4 Objective 4: To determine if gabapentinoid misuse differs based on gabapentinoid type.

Objective 4 was to determine if gabapentinoid misuse differed based on gabapentinoid type (Table 4.5). Overall, there were N = 30,177 (77.4%) gabapentin users and N = 8,823 (22.6%) pregabalin users.

A chi-square test revealed that gabapentinoid misuse was significantly ($X^2 = 13.2$, p = 0.0003) higher among pregabalin users (0.4%) than gabapentin users (0.2%). Therefore, the hypothesis below was rejected.

H_4: The proportion of patients with gabapentinoid misuse is significantly higher in gabapentin users compared to pregabalin users. ***Rejected***

Table 4.5: Chi-square comparison of gabapentinoid misuse among gabapentin users vs pregabalin users (N = 39,000)

Gabapentinoid type	All users N (col %)	Misuse N (row %)	No misuse N (row %)	p-value
Gabapentin	30,177 (77.4%)	49 (0.2%)	30,128 (99.8 %)	0.0003[a]
Pregabalin	8,823 (22.6%)	32 (0.4%)	8,791 (99.6%)	
Total	39,000 (100.0%)	81 (0.2%)	38,919 (99.8%)	

[a] Chi-square test

4.3.5 Objective 5: To determine if gabapentinoid misuse differs between concurrent opioid users and non-concurrent opioid users.

Objective 5 was to determine if gabapentinoid misuse differed between concurrent opioid users and non-concurrent opioid users (Table 4.6). Overall, there were 6,755 (17.3%) gabapentinoid users with at least 90-day concurrent opioid use.

A chi-square test revealed that there was no significant ($X^2 = 2.1$, $p = 0.1440$) difference in gabapentinoid misuse among gabapentinoid users with 90-day concurrent opioid use (0.3%) compared to gabapentinoid users without 90-day concurrent opioid use (0.2%). Therefore, the hypothesis below was rejected.

H_5: *The proportion of patients with gabapentinoid misuse is significantly higher in concurrent opioid users compared to non-concurrent opioid users.* ***Rejected***

A sensitivity analysis revealed that there was no significant ($X^2 = 3.4$, $p = 0.0660$) difference in gabapentinoid misuse among gabapentinoid users with at least 60-day concurrent opioid use (0.3%) compared to gabapentinoid users without 60-day concurrent opioid use (0.2%). Similarly, there was no significant ($X^2 = 3.1$, $p = 0.798$) difference in gabapentinoid misuse among gabapentinoid users with at least 120-day concurrent opioid use (0.3%) compared to gabapentinoid users without 120-day concurrent opioid use (0.2%).

Table 4.6: Chi-square comparison of gabapentinoid misuse among 90-day concurrent opioid users compared to non-concurrent opioid users (N = 39,000)

Concurrent opioid user status	All users N (col %)	Misuse N (row %)	No misuse N (row %)	p-value
Concurrent opioid users	6,755 (17.3%)	19 (0.3%)	6736 (99.7%)	0.1440[a]
Non-concurrent opioid users	32,245 (82.7%)	62 (0.2%)	32183 (99.8%)	
Total	39,000 (100.0%)	81 (0.2%)	38,919 (99.8%)	

[a] Chi-square test

4.3.6 Objective 6: To determine the relationships between likelihood of gabapentinoid misuse and age, gender, neuropathic pain diagnosis, gabapentinoid type and concurrent opioid use.

Objective 6 was to determine the likelihood of gabapentinoid misuse by age, gender, neuropathic pain diagnosis, gabapentinoid type and concurrent opioid use. A logistic regression test revealed that the likelihood of gabapentinoid misuse was significantly associated with age, gender, neuropathic pain diagnosis and gabapentinoid type (Table 4.7).

For every year increase in age, the odds of misusing gabapentinoids decreased by 3.3% (OR = 0.967, 95% CI = 0.949-0.986; p = 0.0007). Therefore, the hypothesis below was rejected.

Ho$_{6a}$: *There is no significant relationship between the likelihood of patients misusing gabapentinoids and age, while controlling for covariates.* ***Rejected***

The odds of misusing gabapentinoids were 51.4% lower for females compared to males. (OR = 0.486, 95% CI = 0.313-0.756; p = 0.0013). Therefore, the hypothesis below was rejected.

Ho$_{6b}$: *There is no significant relationship between the likelihood of patients misusing gabapentinoids and gender, while controlling for covariates.* ***Rejected***

The odds of misusing gabapentinoids were 2.1 times higher for gabapentinoid users with neuropathic pain diagnosis compared to gabapentinoid users without neuropathic pain diagnosis. (OR = 2.065, 95% CI = 1.289-3.308; p = 0.0026). Therefore, the hypothesis below was rejected.

Ho$_{6c}$: *There is no significant relationship between the likelihood of gabapentinoid users misusing gabapentinoids and neuropathic pain diagnosis status, while controlling for covariates.* ***Rejected***

The odds of misusing gabapentinoids were 2.3 times higher for pregabalin users compared to gabapentin users. (OR = 2.337, 95% CI = 1.492-3.661; p = 0.0002). Therefore, the hypothesis below was rejected.

H_{6d}: *Gabapentin users are significantly more likely to misuse gabapentinoids than pregabalin users, while controlling for covariates.* ***Rejected***

The likelihood of misusing gabapentinoids was not significantly associated with concurrent opioid use. (OR = 1.542, 95% CI = 0.920-2.586; p = 0.1006). Therefore, the hypothesis below was rejected.

H_{6e}: *Concurrent opioid users are significantly more likely to misuse gabapentinoids than non-concurrent opioid users, while controlling for covariates.* ***Rejected***

Table 4.7: Logistic regression analysis of gabapentinoid misuse by age, gender, neuropathic pain diagnosis and gabapentinoid type (N = 39,000)

Independent variable	Odds ratio	95% CI	Wald X^2	p-value
Age	0.967	0.949-0.986	11.62	0.0007
Gender: Female	0.486	0.313-0.756	10.27	0.0013
Neuropathic pain diagnosis	2.065	1.289-3.308	9.10	0.0026
Gabapentinoid type: Pregabalin	2.337	1.492-3.661	13.75	0.0002
Concurrent opioid use	1.542	0.920-2.586	2.70	0.1006

Reference groups = males, no neuropathic pain diagnosis, gabapentin, non-concurrent opioid use

Table 4.8: Summary of hypotheses testing

Objectives/Hypotheses	Result
Objective 1: To describe the proportion of Texas Medicaid gabapentinoid users with gabapentinoid misuse.	
Objective 2: To describe and compare the demographic characteristics (age and gender) of Texas Medicaid gabapentinoid users misusing gabapentinoids versus gabapentinoid users not misusing gabapentinoids.	
Ho_{2a}: There is no significant difference in age among gabapentinoid users misusing gabapentinoids versus gabapentinoid users not misusing gabapentinoids.	**Rejected** *Misusers were significantly younger than non-misusers.*
Ho_{2b}: There is no significant difference in gender among gabapentinoid users misusing gabapentinoids versus gabapentinoid users not misusing gabapentinoids.	**Rejected** *A higher proportion of males misused gabapentinoids compared to females.*
Objective 3: To determine if gabapentinoid misuse differs between gabapentinoid users with and without neuropathic pain.	
Ho_3: There is no significant difference in gabapentinoid misuse between gabapentinoid users with and without neuropathic pain.	**Rejected** *Misuse was higher among users with neuropathic pain compared to users without neuropathic pain.*
Objective 4: To determine if gabapentinoid misuse differs based on gabapentinoid type.	
H_4: Gabapentinoid misuse is significantly higher in gabapentin users compared to pregabalin users	**Rejected** *The rate of misuse in pregabalin users was higher than misuse in gabapentin users*
Objective 5: To determine if gabapentinoid misuse differs between concurrent opioid users and non-concurrent opioid users.	
H_5: Gabapentinoid misuse is significantly higher in concurrent opioid users compared to non-concurrent opioid users.	**Rejected** *There was no significant difference in misuse in concurrent opioid users compared to non-concurrent opioid users.*
Objective 6: To determine the relationships between likelihood of gabapentinoid misuse by age, gender, neuropathic pain diagnosis, gabapentinoid type and concurrent opioid use.	
$Ho_{6a:}$ There is no significant relationship between the likelihood of patients misusing gabapentinoids and age, while controlling for covariates.	**Rejected** *For every year increase in age, the odds of misusing gabapentinoids decreased by 3.3%*

Table 4.8: Summary of hypotheses testing continued

$Ho_{6b:}$ There is no significant relationship between the likelihood of patients misusing gabapentinoids and gender, while controlling for covariates.	**Rejected** *The odds of misusing gabapentinoids were 51.4% lower for females compared to males.*
$Ho_{6c:}$ There is no significant relationship between the likelihood of gabapentinoid users misusing gabapentinoids and neuropathic pain diagnosis status, while controlling for covariates.	**Rejected** *The odds of misusing gabapentinoids were 2.1 times higher for gabapentinoid users with neuropathic pain diagnosis compared to gabapentinoid users without neuropathic pain diagnosis.*
$H_{6d:}$ Gabapentin users are significantly more likely to misuse gabapentinoids than pregabalin users, while controlling for covariates.	**Rejected** *The odds of misusing gabapentinoids were 2.3 times higher for pregabalin users compared to gabapentin users.*
$H_{6e:}$ Concurrent opioid users are significantly more likely to misuse gabapentinoids than non-concurrent opioid users, while controlling for covariates.	**Rejected** *The likelihood of misusing gabapentinoids was not significantly associated with concurrent opioid use.*

Chapter 5: Discussion and Conclusions

5.1 CHAPTER OVERVIEW

This chapter contains the discussion of the study results and it is divided into four sections. The first section covers a discussion of study results in light of the current literature. The second section discusses the study limitations, the third section cover suggestions for future research while the final section includes the study conclusions.

5.2 DISCUSSION OF STUDY FINDINGS

5.2.1 Objective 1

The purpose of objective 1 was to quantify the proportion of Texas Medicaid gabapentinoid users with gabapentinoid misuse. Only 0.2% of the study population met the criteria for gabapentinoid misuse. While studies exist regarding gabapentinoid use and misuse, there are limited retrospective database studies that focus on prevalence of gabapentinoid misuse. One such study, by Peckham et.al., used the Truven Health MarketScan® commercial database where they defined misuse as having three or more pharmacy claims that exceeded the recommended daily threshold. This definition is similar to our definition of misuse, however, the prevalence of gabapentinoid misuse in their study was higher than ours (2.7%).[61] The authors indicated (personal communication) that the database captured all prescription transactions including cash payments. The database also included multiple claims from different prescribers and filled at multiple pharmacies. Thus, their study potentially captured doctor and pharmacy shopping and patients getting prescriptions from multiple sources. Whereas in our study, Medicaid policies may preclude patients from obtaining: early prescription refills, multiple prescriptions for the same

medication, or prescriptions that consistently exceed FDA approved doses.[147, 148] Thus, a contributor to the difference in our study results and those using the Truven database may be stricter Medicaid policies, as well as the inability to capture cash paying prescriptions in the Medicaid database. Also, misuse may be underestimated in any study if patients obtain these medications outside of the healthcare network. Studies have shown that a significant percentage of access to gabapentinoids, specifically gabapentin, may be outside of legitimate doctor/pharmacy relationships.[60, 118, 131, 132] A qualitative study conducted in Kentucky found that about 36% of access to gabapentin could be attributed to illegal drug purchases.[131, 132] Finally, it is also possible that gabapentinoid misuse is not prevalent among Texas Medicaid recipients. It is unclear if the prevalence of gabapentinoid misuse differs among various patient populations.

5.2.2 Objective 2

Objective 2 was to describe and compare the age and gender of Texas Medicaid gabapentinoid users misusing gabapentinoids versus gabapentinoid users not misusing gabapentinoids. In this study, the mean (±SD) age of subjects was 48.2 (±10.7). The mean (±SD) age of non-misusers was the same as the overall mean age of all subjects. However, the mean (±SD) age of misusers was 45.1 (±11.0), and this was significantly lower than non-misusers. The mean age of subjects in this study was only slightly lower than the participants in the Truven study, as gabapentin and pregabalin users had a mean (±SD) age of 50 (±11.0) and 49 (±9.0), respectively.[25] In the FAERS study by Evoy et. al., the mean (±SD) age for all patients with gabapentin adverse events was 56.2 (±15.6). However, the mean age was lower [46.6 (±17.1)] for abuse-related events. Similarly, for pregabalin, the overall mean (±SD) age for adverse events was 48.9 (±16.3) but for abuse-related events,

the mean (±SD) age was lower [36.1 (± 12.7)].[59] A study conducted in Sweden found that pregabalin misuse was associated with younger (18 to 29 years old) rather than older (≥ 65 years old) adults.[149] The role of age in gabapentinoid misuse is not clear but studies have found an association with younger age and gabapentinoid misuse/abuse.[25, 59, 126] While our study supported this trend, it is important to note that the difference in age between users and misusers (~3 years) may not be practically significant.

With respect to gender, there was a higher proportion of females (68.1%) than males in the study sample. However, there was a significantly higher proportion of misuse among males (0.3%) compared to females (0.2%). The results regarding gender cannot be compared to other studies as the distributions of misuse between females and males have been inconsistent across studies.[12, 26, 129] Note that although statistically significant, the difference was minimal and not likely practically significant.

5.2.3 Objective 3

Objective 3 was to determine if gabapentinoid misuse differs between gabapentinoid users with and without neuropathic pain. Among other conditions, gabapentin and pregabalin are both indicated for the management of neuropathic pain.[8, 14] Gabapentin and pregabalin have demonstrated effective neuropathic pain management in different studies.[9, 150] About 52% (N = 20,247) of our study sample had a neuropathic pain diagnosis. The number of gabapentinoid misusers with neuropathic pain diagnoses was two times higher than those without (N = 54 vs. N=27, respectively). A chi-square test revealed that gabapentinoid misuse was significantly higher in patients with neuropathic pain diagnosis (0.3%) compared to patients without neuropathic pain diagnosis (0.1%). Although the differences in proportion (0.3% vs 0.1%) may be considered minimal similar

to results regardin gender, the size of the groups being compared in this objective is almost equal (52% vs 48%) making the differences in proportion practically meaningful.

Currently, there is a paucity of research comparing gabapentinoid misuse specifically in patients with and without neuropathic pain diagnosis. The results of our study may indicate gabapentinoid misuse may not always be the result of irresponsible use but possibly due to the need for higher pain management in patients with neuropathic pain. This consideration is especially important in quantitative studies where factors such as pain level may not be easily extrapolated from medical and prescription claims data.

5.2.4 Objective 4

Objective 4 was to determine if gabapentinoid misuse differs based on gabapentinoid type. The gabapentinoids evaluated in this study were pregabalin and gabapentin. Pregabalin was first approved in 2004 for the treatment of diabetic peripheral neuropathy and postherpetic neuralgia.[11, 12] Gabapentin was first approved in 1993 as an adjunct treatment for partial complex seizures in people over 12 years old. This approval was later extended to include treatment for postherpetic neuralgia in 2002.[113] Pregabalin was classified as a schedule V controlled substance by the DEA at the time of its release, while gabapentin is not classified as a controlled substance federally because it was believed to have a low potential for abuse.[13] However, with evidence showing exponential increases in gabapentin prescribing and its presence in overdose and autopsy reports, concerns about the potential for misuse and abuse with gabapentin is increasing.[14, 15, 26, 35, 59, 133] About 26 years after gabapentin was first approved, the FDA is now requiring manufacturers to conduct clinical trials evaluating the abuse potential of gabapentinoids.[135,

[136] Currently, 7 states have made gabapentin a schedule V controlled substance and at least 8 other states require monitoring of gabapentin prescribing and dispensing.[60,33, 34, 140, 141]

The goal of this objective was to determine if gabapentinoid misuse differs based on gabapentinoid type. In this study, 77.4% (N = 30,177) of the sample were gabapentin users, while 22.6% (N= 8,823) were pregabalin users and a chi-square analysis revealed that the proportion of misuse among pregabalin users (0.4%) was significantly higher than gabapentin users (0.2%). This was different from our hypothesis, as we expected the proportion of misuse among gabapentin users to be higher than among pregabalin users. We had this expectation because unlike pregabalin, gabapentin is not controlled at the federal level. Also, some studies show increasing evidence of gabapentin prescribing and misuse.[14, 15, 35, 59] However, other studies have shown higher proportion of misuse among pregabalin users compared to gabapentin users.[59, 129]

In the Eudravigilance pharmacovigilance study, 6.6% of pregabalin adverse events reports were attributed to misuse, abuse and dependence while 4.8% of gabapentin adverse events reports were attributed to misuse, abuse and dependence.[129] The pattern in our study may be comparable to the pattern observed in the FAERS study by Evoy et. al.[59] In their study, a substantially higher number of gabapentin adverse events (N = 10,038) were identified compared to pregabalin (N = 571). However, the proportion of these reports related specifically to abuse was higher in pregabalin (10%) than gabapentin (5.7%). While evidence shows that gabapentin prescribing and misuse is increasing, [14, 15, 35, 59] the gabapentinoid with a higher proportion of misuse in our study population was pregabalin. Similar to other studies, our study shows that gabapentinoid misuse differs based on gabapentinoid type and is significantly higher among pregabalin users than gabapentin users in this population.

5.2.5 Objective 5

Objective 5 was to determine if gabapentinoid misuse differs between concurrent opioid users and non-concurrent opioid users. The concern about gabapentinoid misuse significantly increases when there is concurrent opioid use. Some studies suggest that overdose of gabapentinoids alone may not have lethal effects but when used in combination with opioids or sedatives, side effects of opioid overuse such as respiratory depression can increase up to 60%. [60, 118, 126, 138]

In this study, about 57% (N = 22,102) of patients used opioids concurrently for at least one day. This is comparable to what was observed in the IBM Marketscan® database study by Pauly et. al. They found that about 61% of people who have been prescribed gabapentin had at least one opioid prescription.[35] Similarly, a case control study in Canada found that about 46% of gabapentin users had at least one concurrent opioid prescription, and this concurrent use increased opioid-related fatality by 49%. [107]

Further analysis of our data revealed that 23% (N = 9,147), 17% (6,755) and 13% (5,139) of gabapentinoid users had concurrent opioid use for at least 60, 90 and 120 days, respectively. Based on previous studies, we expected the proportion of concurrent opioid users to be higher. Also, there was no significant difference in gabapentinoid misuse among concurrent opioid users for at least 90 days (0.3%) compared to non-concurrent opioid users for at least 90 days (0.2%). A sensitivity analysis was performed to determine how misuse differed among concurrent opioid users for at least 60 days and 120 days. However, results of the sensitivity analysis showed that there was no significant difference in misuse among both the 60-day and 90-day concurrent opioid users and non-concurrent opioid users.

These results were unexpected because previous studies suggest that opioid use is a risk factor for gabapentinoid misuse. Gabapentinoids have been found to potentiate the

"high" obtained from opioid use which can lead to increased gabapentinoid misuse in concurrent opioid users.[126, 130, 131, 132] In the Truven® database study by Peckham et. al., the authors found that about 22% of gabapentin users and 26% of pregabalin users had concurrent opioid use for at least 120 days within a 12-month period. [25] They also found that 24% of patients who had both gabapentin and opioid prescriptions, and 28% of patients who had both pregabalin and opioid prescriptions had no less than three pharmacy claims that exceeded recommended dosage limits, in contrast to 3% of patients on gabapentin alone, 5% of patients on pregabalin alone and 8% of patients on opioids alone.[25]

In another study where the authors categorized gabapentin overuse into mild and sustained, they found that only 2% of patients on gabapentin alone met their prolonged overuse criteria but 11% of patients on both gabapentin and opioids met the prolonged overuse criteria. Prolonged overuse was defined as exceeding dosage threshold for three or more "rolling" calendar quarters. While their definition for overuse/misuse in this study was different from ours, they found that there were more concomitant opioid users who met the prolonged overuse criteria compared to those who did not use opioid concomitantly.[111]

5.2.6 Objective 6

The goal of Objective 6 was to determine the likelihood of gabapentinoid misuse by age, gender, neuropathic pain diagnosis, gabapentinoid type and concurrent opioid use, while controlling for remaining covariates. The results of the logistic regression were consistent with the observations in our bivariate analysis for the above objectives.

We observed that, the likelihood of gabapentinoid misuse decreases with an increase in age; females were less likely to misuse gabapentinoids compared to males;

patients with neuropathic pain diagnosis were twice as likely to misuse gabapentinoids compared to patients without neuropathic pain diagnosis; pregabalin users were also twice as likely to misuse gabapentinoids compared to gabapentin users; and finally, the likelihood of misusing gabapentinoids was not significantly associated with concurrent opioid use.

5.3 IMPLICATION OF FINDINGS

Our findings suggest that Texas Medicaid has policies in place that limit the misuse of gabapentinoids. However, there is still some amount of misuse that can be further evaluated. For clinicians, this study sheds light on the possibility and presence of gabapentinoid misuse. While this may not be considered a pressing problem among Texas Medicaid recipients, an understanding of gabapentinoid misuse and potential related suboptimal outcomes would be informative for clinicians. For Texas Medicaid recipients, this study creates awareness regarding the potential for misusing gabapentinoids. Awareness on the possibility of misuse and consequences would be beneficial for this group.

5.4 STUDY LIMITATIONS

The purpose of this study was to assess the prevalence and factors associated with gabapentinoid use and misuse among Texas Medicaid recipients. Some limitations that may affect the study results are discussed below. First, the risk of error associated with retrospective database studies may impact our results. This study depended on the accuracy of prescription days' supply to define misuse and diagnosis codes to determine indications for neuropathic pain. The possibility for entry or misclassification errors can lead to

exclusion or improper classification. Second, patients were evaluated based on either gabapentin or pregabalin misuse, thus omitting those who may have used both gabapentin and pregabalin (N~7,700 in the present study) There is a possibility that patients who may not have met the criteria for misuse based on only one medication, may have been classified as misusers if dual therapy were considered. Thus, the prevalence of misuse may have been underestimated. Third, we may not have captured the total medication use of patients within the study period as gabapentinoids can be accessed outside legitimate doctor/pharmacist network. This information is not usually captured in claims data. Also, other relevant factors related to medication use or misuse such as pain level, tobacco and alcohol use, and previous incarceration may not be easily obtained from claims and diagnosis data, but may be important in assessing reasons or predictors of misuse. Finally, the study was limited to only Texas Medicaid recipients and may not be generalizable to a different socio-economic or demographic groups nor other state Medicaid programs.

5.5 SUGGESTIONS FOR FUTURE RESEARCH

The main purpose of this study was to examine the prevalence of and factors associated with gabapentinoid use and misuse among Texas Medicaid recipients. This study utilized a retrospective database analysis to achieve this purpose. However, a limitation of this method is that gabapentinoids accessed outside the legitimate doctor/pharmacist network was not captured. Future qualitative studies may shed light on the possibility of gabapentinoid use and misuse outside this network.

Gabapentinoid misuse research is an emerging area, and as such, gaps of knowledge exist in the literature. It is not yet clear the role age, gender or socioeconomic status plays in gabapentinoid misuse. In the Pauly et al., study, the authors observed disparities in

gabapentin prescribing across different states with Kentucky and Washington DC., having the highest (43.9 per 1000 beneficiaries) and lowest (12.7 per 1000 beneficiaries) prescribing rates, respectively.[35] It is not clear why these disparities occur across different states. Further research into the role of demographic and environmental characteristics can provide useful information for intervention strategies.

Also, the discovery of significantly higher misuse among patients with a neuropathic pain diagnosis (compared to those with no diagnosis) may provide subsequent research foci.

5.6 CONCLUSION

Studies have shown an increase in the utilization rates of gabapentin and pregabalin within the last few years. Also, the potential for misuse and abuse of gabapentinoids have become a public health concern. As a result, several states have adopted some type of mechanism to monitor and control gabapentinoid prescribing.

Our study showed that the prevalence of gabapentinoid misuse was low among Texas Medicaid recipients, as only 0.2% misused gabapentinoids. We discovered that gabapentinoid misuse was more prevalent among younger adults, males, patients with neuropathic pain diagnosis and pregabalin users. Unexpectedly, gabapentinoid misuse was not significantly associated with concurrent opioid use. However, our study results are generalizable to only Texas Medicaid recipients.

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